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IN TWO SECTIONS — SECTION I

DECEMBER 1955

VOLUME 74 NUMBER 6

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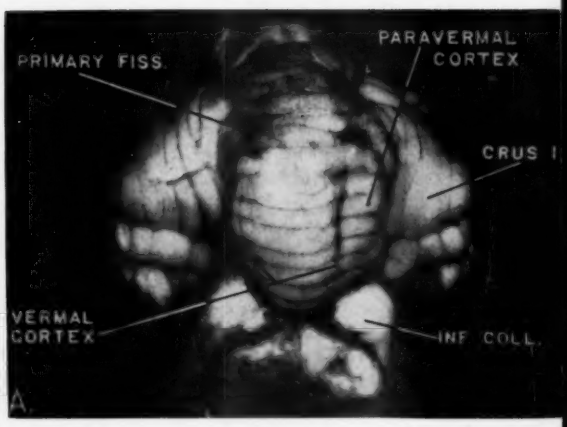

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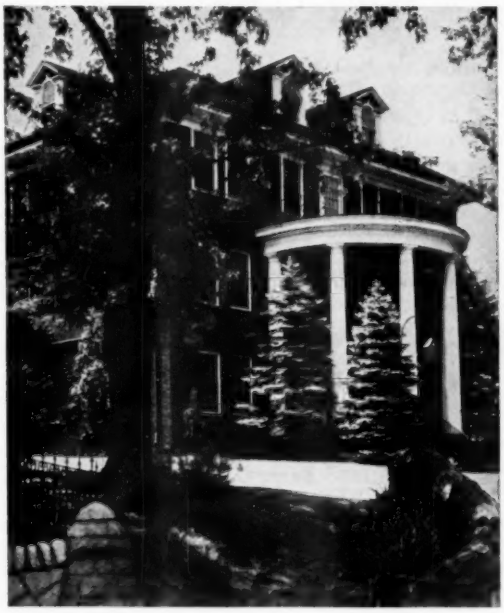

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Right-Left Discrimination and Finger Localization in Defective Children

ARTHUR L. BENTON, Ph.D., Iowa City

While right-left disorientation and finger agnosia in adult patients have been described in numerous case reports since the publication of the original descriptions of these perceptual deficits by Obersteiner and by Gerstmann, there have been relatively few observations made on their occurrence in children. In 1938 Strauss and Werner,[1] utilizing a test battery which assessed both finger localization and right-left discrimination, reported a relationship between arithmetic achievement and performance on this test battery in a group of subnormal, brain-injured boys. This conclusion seemed to be in accord (or, at least, not in variance) with expectations, in view of the frequent concomitance of impairment in these abilities in the Gerstmann syndrome. However, Benton, Hutcheon, and Seymour,[2] reexamining the question, were unable to confirm the contention of a specific association between these somatoperceptual skills and arithmetic achievement. Moreover, an analysis of the Strauss-Werner data indicated that no strong evidence for the association was actually secured in the original study.

The study by Benton, Hutcheon, and Seymour did yield certain suggestive findings when normal children and institutionalized mental defectives of roughly similar mental age were compared. Utilizing the performances of the normal children as a standard, a relatively small, but clinically significant, proportion of defective children made grossly defective performances—on a level which could reasonably be designated as being "pathologically poor." Another finding of some theoretical interest was that finger-localization and right-left discrimination showed a small, but statistically significant, degree of association with each other, thus suggesting that perhaps there is a basic common factor in at least these two elements of the Gerstmann syndrome, as has been asserted by some writers.*

However, this study was of a preliminary character, and the findings could be regarded only as extremely tentative. The number of cases involved was small; the normal and pathological groups were not precisely matched with respect to mental age level, and no attention was paid to the specific category of mental deficiency represented by the patient, the assumption being made that, by definition, mental deficiency implied brain injury. It was evident that a first step in the confirmation of these preliminary results would be the establishment of adequate standards of performance for normal children of different mental age levels, with which the performances of brain-injured

Received for publication June 13, 1955.

From the Department of Psychology, State University of Iowa, and the Woodward State Hospital, Woodward, Iowa.

* References 3 and 4.

children of the same mental age levels could be compared. Accordingly, normative investigations, the findings of which have been published,† were carried out. With the standards provided by these normative investigations as a basis for comparison, a study of the performances of brain-injured children was done, the results of which are here reported.

METHOD AND MATERIAL

Subjects.—The main group of subjects consisted of 35 patients at the Woodward State Hospital in the diagnostic classification of "mental deficiency—brain injury" (trauma, infection, neoplasm). The range of ages was 11-22 years, the mean age being 15.3 years. The range of mental ages was 6-9 years, the mean mental age being 7.6 years. The range of intelligence quotients (Stanford-Binet or Wechsler-Bellevue) was 40-75, the mean intelligence quotient being 53.9. There were 11 male and 24 female subjects in the group.

A second group of subjects consisted of 35 patients in the diagnostic classification of "mental deficiency—familial." The range of ages was 9-22 years, the mean age being 16.9 years. The range of mental ages was 6-9 years, the mean mental age being 7.4 years. The range of intelligence quotients was 40-65, the mean intelligence quotient being 52.5. There were 12 male and 23 female subjects in the group.

A third group of subjects consisted of 40 patients in the diagnostic classification of "mental deficiency —undifferentiated," i. e., of unknown etiology. The range of ages was 10-22 years, the mean age being 16.7 years. The range of mental ages was 6-9 years, the mean mental age being 7.1 years. The range of intelligence quotients was 40-68, the mean intelligence quotient being 50.4. There were 17 male and 23 female subjects in the group.

When the three groups were combined into a single group, of 110 cases (as was justifiable in view of their similarity in personal characteristics and, as will be seen, their similarity with respect to performance), the characteristics of the total group were as follows: mean age, 16.3 years; mean mental age, 7.4 years; mean intelligence quotient, 52.2.

Test Batteries.—The right-left discrimination test battery utilized in the investigation consisted of 20 items, as follows:

Item — Task

1-6: With his eyes open, patient points to parts of his body named by examiner (e. g., right eye, left hand, right ear).

7-10: Patient points to body parts in front-view representation of a boy (e. g., boy's right hand, boy's left eye).

11-14: With his eyes open, patient executes "crossed commands" with reference to his own body (e. g., right hand on left eye, left hand on right eye).

15-18: With his eyes closed, patient points to parts of his body named by examiner.

19-20: With his eyes closed, patient executes "crossed commands" with reference to his own body.

Score on the test was defined as the number of consistent discriminations, regardless of the correctness of the responses with respect to the verbal symbols "right" and "left" (i. e., if a patient consistently showed the left body part when asked to show the right, and vice versa, he would make a perfect score). This type of scoring was adopted because some patients showed evidence of considerable somatospatial discriminative ability, with, however, complete reversal with respect to the symbols "right" and "left." Since we were interested in the discriminative ability per se rather than in the appreciation of conventional verbal symbols, this "discrimination-consistency" score seemed superior, on logical grounds, to a score which took account of the absolute correctness of the single responses. In the majority of cases (80%), the two scores proved to be the same.

The finger-localization test battery consisted of 50 items, as follows:

Item — Task

1-20: With his hand visible to him, the patient names (or points to) single fingers which have been tactually stimulated with the end of a pencil in predetermined random order; 10 trials each hand.

21-40: With his hand hidden from his view, the patient names (or points to) single fingers which have been tactually stimulated; 10 trials each hand.

41-50: With his hand hidden from his view, the patient names (or points to) pairs of fingers which have been subjected to simultaneous tactual stimulation; 5 trials each hand.

In order to eliminate the necessity for (but not the possibility of) verbal responses on the part of the patient, a model of the right or left hand, with the thumb and fingers numbered from 1 to 5, was placed before him. He was then told that he could identify the stimulated finger (or fingers) by naming it ("thumb," "little finger," etc.), by indicating its number on the model, or simply by pointing to it on the model.

The patient placed his hand on the table, palm up with the fingers extended and slightly spread.

† References 5 and 6.

TABLE 1.—*Critical Scores on Right-Left Discrimination and Finger Localization Tests*

Mental Age, Yr.	Score: Right-Left Discrimination	Score: Finger Localization
6	9	22
7	10	25
8	14	33
9	15	36

In finger localization without the aid of vision, a wooden box, from which the front and back sides had been removed and to the front side of which a curtain had been attached, was utilized. The patient inserted his hand behind the curtain of the front side while the experimenter stimulated individual fingers through the open back side.‡

Scoring was on an "all-or-none" basis, a credit of one point being given for each correct indentification. On the 10 trials involving simultaneous stimulation of two fingers, both fingers had to be identified correctly in order for the response to be counted as correct.

Normative Standards.—Critical scores, derived from the findings of the normative investigations,§ served as a standard against which the performances of the patients were compared. These critical scores represent performance levels which are reached or exceeded by at least 95% of normal children of the respective mental ages. Therefore, a performance level below that indicated by the appropriate critical score was interpreted as being pathologically defective. These critical scores are presented in Table 1.

‡ See Benton [6] for a graphic illustration of the arrangement for finger localization without the aid of vision.

§ References 5 and 6.

TABLE 2.—*Right-Left Discrimination Scores*

Category of Mental Defect		Mental Age: 6 Yr.	7 Yr.	8 Yr.	9 Yr.
"Brain Injury"	Mean	12.33	13.67	14.89	16.63
	S. D.	1.92	2.48	3.84	2.72
	N	3	15	9	8
"Familial"	Mean	12.82	14.14	14.13	15.67
	S. D.	2.86	3.00	2.15	2.29
	N	11	7	8	9
"Undifferentiated"	Mean	13.24	14.00	14.67	16.57
	S. D.	3.26	3.82	3.28	3.07
	N	17	7	9	7
All defectives	Mean	13.00	13.86	14.58	16.25
	S. D.	3.17	2.95	3.21	2.68
	N	31	29	26	24
Normative sample	Mean	13.08	16.24	17.29	18.31
	S. D.	3.09	2.81	1.99	1.82
	N	40	41	38	39

RESULTS

GROUP DIFFERENCES IN PERFORMANCE

The mean scores of the three groups of patients on the right-left discrimination test are shown in Table 2. It will be seen that at each mental age level the differences in mean score are minimal and the direction of the differences is not consistent from one mental age level to another. The scores for the three clinical subgroups were therefore combined, and means for the total defective group for each mental age level were computed. These mean scores are also presented in Table 2. In addition, for comparative purposes, the mean scores of the normal children in our earlier study [5] are included in the Table.

It will be noted that at each mental age level the mean score of the defective group is inferior to that of the matched normal group. The difference in the mean scores is minimal at the 6-year mental age level. However, at the other three mental age levels the differences are of more impressive magnitude and are statistically significant, as estimated by the *t*-test.

Similarly, the mean scores of the three groups of patients on the finger localization test are shown in Table 3. At any given mental age level the differences in score

TABLE 3.—*Finger Localization Scores*

Category of Mental Deficiency		Mental Age: 6 Yr.	7 Yr.	8 Yr.	9 Yr.
"Brain Injury"	Mean	25.00	30.13	38.33	40.38
	S. D.	9.27	6.06	7.50	4.69
	N	3	15	9	8
"Familial"	Mean	29.82	31.43	33.12	37.89
	S. D.	8.16	8.80	8.90	4.77
	N	11	7	8	9
"Undifferentiated"	Mean	26.71	32.43	36.89	40.71
	S. D.	7.87	8.09	2.88	2.81
	N	17	7	9	7
All defectives	Mean	27.65	31.00	36.23	39.54
	S. D.	8.29	7.38	6.97	4.45
	N	31	29	26	24
Normative sample	Mean	34.88	40.10	42.61	44.61
	S. D.	5.84	5.36	4.08	3.67
	N	40	41	38	39

among the diagnostic subgroups are small and inconsistent with respect to direction of difference. The scores for the total defective group and for the normative group of children [6] are also shown in Table 3. A consistent difference in the mean scores of the defective and normal groups is evident. At each mental age level the difference is statistically significant, as estimated by the *t*-test.

Incidence of Defective Performance

Since clinical interest is centered on the performances of individuals rather than on statistically determined group differences, an analysis of the proportions of patients in each group who showed defective performance was made.

Right-Left Discrimination.—In Group I ("Mental Deficiency—Brain Injury"), 6 patients (17%) out of 35 made defective performances, on the basis of the critical scores. The patients in Group II ("Mental Deficiency—Familial") showed a 20% incidence of defective performance (7 out of 35 cases). In Group III ("Mental Deficiency—Undifferentiated"), 7 patients (18%) out of 40 made defective performances. Since the incidence of defective performance did not differ significantly among the three diagnostic groups, the figures were combined, yielding an over-all incidence of defective performance of 18.2% (20 out of 110 cases). On the basis of the normative findings, about six cases would have been expected to perform on a defective level.

Finger Localization.—In Group I ("Mental Deficiency—Brain Injury"), 8 (23%) of the 35 cases made defective performances. In Group II ("Mental Deficiency—Familial"), 10 (29%) made defective performances. In Group III ("Mental Deficiency—Undifferentiated"), 8 (20%) of the 40 cases made defective performances. When the figures for the three groups are combined, an incidence of defective performance of 24.5% (26 cases out of a total of 110) is found. On the basis of the findings of the normative investigation, about four defective performances would be expected.

Relation Between Right-Left Discrimination and Finger Localization

The relationship between right-left discrimination and finger localization was estimated by computing product moment correlation coefficients between the several variables involved, i. e., the two functions, age and mental age. For the purposes of this analysis, the number of cases was augmented to 121 by the addition of 11 cases within the mental age range of 9 years 6 months to 10 years 5 months. The results of this analysis, as well as those of a similar analysis of the normative group, are shown in Table 4.

Table 4.—*Product Moment Correlation Coefficients Between Right-Left Discrimination and Finger Localization Performances*

Variables

1. Right-left discrimination
2. Finger localization
3. Chronological age
4. Mental age

	Normative Group (N = 158)		Defectives (N = 121)	
Variables	*r*	*p*	*r*	*p*
12	0.49	0.001	0.54	0.001
12.3	0.22	0.006	0.54	0.001
12.4	0.24	0.003	0.39	0.001
12.34	0.21	0.009	0.40	0.001

It will be noted that right-left discrimination and finger localization show a significant degree of association in both groups. This relationship is maintained even when the effects of age and mental age are partialed out. However, from a quantitative point of view, the degree of association is of rather small magnitude, although highly significant.

COMMENT

The findings indicate that, when the performances of younger normal children of comparable mental age are used as a standard, there is a considerable incidence of impairment in performance in defective children on tasks involving right-left discrimination and finger localization. If "impairment" is defined as a performance below the level which is reached or exceeded by at least 95% of normal children of the appropriate

mental age, one finds that about 18% of the pathological subjects perform defectively in the area of right-left discrimination and about 25% perform defectively in the area of finger localization.

It is of some interest that mental defect states of supposedly different etiology are not discriminated by performance on these tasks. A number of reports in the literature, dealing mainly with characteristics of psychologic test performance, might lead one to expect that the "brain-injured" defective patients would behave differently from the "familial" defective patient, who should show a rather unremarkable performance, similar to that of a younger normal child of the same mental age. However, such is not the case with respect to the particular functions investigated in the present study. "Brain-injured" defective patients and those with "familial" and "undifferentiated" mental defects show a virtually equal incidence of defective performance, and the magnitude of this incidence is far above expectations based on a concept of simple retardation. In isolation, these findings carry no great significance, but it is noteworthy that they are in accord with a body of neurologic, neuropathological, and psychologic data,‖ all of which suggest that the dichotomy of "familial" versus "brain-injury" mental defect stands on a rather insecure empirical foundation and that the concept of "familial" or "simple" mental deficiency as a mere arrest in neuropsychologic development is hardly tenable.

Clinical experience suggests that isolated impairment in right-left discrimination and finger localization is a relatively uncommon finding in adult patients with cerebral disease. The present results with defective children stand in apparent contrast to this impression in that roughly 20% of the children showed what may reasonably be designated as pathologically poor performances, even in relation to their low mental ages. This discrepancy in findings may well be due to a difference in the methods used to investigate the functions. The relatively brief right-left discrimination and finger localization test batteries employed in the present study seem simple enough, but they are more elaborate and refined (in the sense of yielding a quantitative index of degree of defect) than those typically utilized in the clinical neurologic examination, which probably disclose only gross perceptual deficits. However, it is also possible that the observed difference in incidence is quite real and essentially independent of the methods of evaluation.

An answer to this question is provided by the results of a preliminary study of the incidence of defective right-left discrimination and finger localization in adult brain-injured patients which employed the same test batteries as were used in the present investigation.[11] In this study the performances of 22 brain-injured patients, all of whom had intelligence quotients of 90 or above, were compared with those of a similar group of control patients. None of the brain-injured patients showed defective right-left discrimination. On the other hand, four patients (18%) showed defective finger localization, their scores being below that of the poorest normal subject. It is noteworthy, however, that the performances of these four patients were not seriously defective by the usual clinical criteria, most of their errors occurring on the double stimulation task.

It appears, then, that with respect to right-left discrimination there is a real difference in the incidence of defective performance in adult patients with relatively recently acquired cerebral injury as compared with children suffering from congenital or early acquired cerebral injury. Isolated right-left disorientation is a relatively uncommon finding in adult patients, and such neuropathological data as are available suggest a localization of the responsible lesion in the parietal lobe of the dominant hemisphere in right-handed patients.[4] Thus, a focal lesion with a particular localization seems to be a prerequisite for the appearance of isolated right-left disorientation in these patients.

‖ References 7 to 10.

We encounter a somewhat different situation in brain-injured children with congenital or early acquired cerebral pathology. The incidence of defective right-left discriminative ability is much commoner. But we deal here not with loss of an acquired skill, as in the adult patient with relatively recent cerebral pathology, but with a failure in the original development of the perceptual skill. The relatively high incidence of defective performance would seem to argue against a highly specific localization of the responsible lesion, such as has been determined to be the rule in adults suffering from a loss in the ability. It is possible that defective right-left discrimination in patients with early acquired cerebral disease does have some broad localizing significance, perhaps in terms of a predominant localization of the lesion in one hemisphere or the other. This is a question which deserves further investigation. But, even if this should prove to be the case, it is evident that the localizing implications are different in the two cases. In the case of the strongly established perceptual skill (as in the adult with recently acquired cerebral pathology), loss of the habit implies a highly specific cerebral localization of the responsible lesion. In contrast, in the case of the undeveloped or developing skill, the cessation of further development implies at most a broad cerebral localization of lesion.

The finger localization results seem to present a rather different picture. A clinically important proportion of patients of both types, i. e., those with recently acquired pathology and those with congenital or early acquired pathology, show defective performances. Thus, the relatively refined examination procedure utilized in this and in our previous studies does disclose mild "finger agnosia" in a small, but nevertheless important, proportion of brain-injured adult patients. The incidence of defective performance appears to be somewhat smaller in this group than in the defective patients, but the number of cases examined is as yet too small to permit a definitive estimate.

The finding of a significant degree of association between right-left identification and finger localization confirms our preliminary results [2] in this regard. This finding offers some support for the contentions of those clinical theorists who view both abilities (as well as writing and calculation) as expressions of a single basic process, such as a "sense of direction in space," the "body schema," or a general praxic skill.¶ However, it must be pointed out that the finding is actually no more supportive of such a unitary type of interpretation than it is of a point of view which would explain the observed association on a topographic basis, i. e., on the supposition of a close proximity of the cerebral foci which are critically involved in the mediation of these perceptual skills. In any event, it is well to keep in mind that the observed degree of association is quite low and can account for only a small part of the variance in both skills.

The potential clinical significance of the findings of the present investigation deserves comment. Since as yet only preliminary observations of children with verified brain injury who are within the normal range of intelligence have been made, no generalizations can be made at this time. However, if it should be found that in this group of children there is a significant incidence of defective performance, as compared with normal children of similar mental age, the results could provide a basis for psychodiagnostic procedures designed to aid in the evaluation of suspected brain injury in children.

SUMMARY

A study of right-left discrimination and finger localization in defective children yielded the following results:

1. As compared with the performances of normal children of matched mental age, there is a clinically significant incidence of poor performance in defective subjects.

2. There is no significant difference in the incidence of poor performance in subjects

¶ References 3 and 4

with "familial" mental defects as compared with that in "brain-injured" defective subjects.

3. Right-left discrimination and finger localization show a small, but statistically significant, degree of association with each other.

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The Effect of Mephenesin on Muscle Tension

An Experimental Study

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Since mephenesin was introduced as a muscle relaxant by Berger and Bradley,[1] in 1946, there have been many clinical reports concerning its use in spastic and hyperkinetic states.* No uniformity was noted in regard to its efficacy in the treatment of these disorders. More recently, the use of mephenesin was extended to the treatment of anxiety states.† Once again, ensuing clinical reports concerning its efficiency in alleviating anxiety were of varying degrees of enthusiasm.‡ The increase of muscle tension in anxiety states is well known. To our knowledge, there have been no quantitative studies of muscle tension responses after the administration of mephenesin in humans. We therefore felt it would be useful to study quantitatively muscle tension in anxious people and to report whether or not mephenesin could be shown to reduce muscle tension, in a predictable fashion.

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† References 2, 5, 7, 8, 19, 22, and 23.

‡ References 2, 5, 7, 8, 19, 22, 23, and 25.

Anxiety is a subjective state associated with physiologic changes, which may be recorded. Numerous investigators § have reported changes in muscle tension in response to varying stimuli and have indicated that muscle tension is a good index of anxiety and emotional upset. Since mephenesin is described as a muscle relaxant, systematic recording of muscle tension provides a useful means of studying this drug.

Tachistoscopic || presentation of words was selected as a visual stimulus to induce anxiety and muscle tension. This stimulus is a nonphysically traumatic, nonchemical modality. McGinnies,[16] Bruner and Postman,[3] and others have demonstrated in their tachistoscopic studies that emotionally charged words have higher thresholds of perception than neutral words. Lazarus and McCleary [11] exposed nonsense syllables and conditioned their subjects to half of these syllables, using electric shock as the unconditioned stimulus. Thresholds of perception were higher for these conditioned syllables than for nonconditioned syllables. There was an increased sweating response for the conditioned syllables, as measured by a psychogalvanic reflex apparatus. Thus, emotionally charged stimuli were recognized at higher thresholds of perception and were associated with physiologic changes, i. e., increased sweating. In the present study, McGinnies', and Bruner and Postman's method has been applied to muscle tension phenomena.

METHOD

Thirty male and female psychiatric outpatients, between the ages of 19 and 43, were selected from

§ References 6, 9, 10, 12, 15, and 18.

|| We used a projector with an electronic timing device to control the duration of exposure of the stimulus words. This was devised and built in our department.

the Kings County Hospital mental hygiene clinic. Each subject was interviewed by a psychiatrist to eliminate overtly psychotic patients and to estimate clinically the degree of anxiety and muscle tension present.

Anxiety was quantitated according to a four-point rating scale as follows:

1+: A vague sense of uneasiness and apprehension which is elicited only through questioning

2+: An increased sense of uneasiness and apprehension of such intensity as to be volunteered by the patient

3+: Symptoms of uneasiness and apprehension together with objective signs of moderate visceromotor disturbances

4+: Progression of all symptoms and signs to the point where visceromotor disturbances become leading presenting symptoms and the subjective anxiety approaches panic

In addition, the psychiatrist estimated the muscle tension expression of anxiety, inasmuch as this was our primary interest in arranging matching groups.

Since the stimulus used in the test was a visual one presented by the tachistoscope, adequate vision was insured by having the patients read a Snellen eye chart. Prospective subjects with poor vision were eliminated from the study.

Thirty subjects with acceptable levels of vision were divided into two groups of 15 each, so that the clinically estimated mean muscle tensions of the two groups were almost identical. One group received 3.0 gm. of mephenesin, and the other group were given a placebo made up in identical fashion. Neither the subjects nor the investigators knew which was the active preparation until the conclusion of the entire series. These preparations were administered 40 minutes before the beginning of the test to allow for absorption from the gastrointestinal tract.

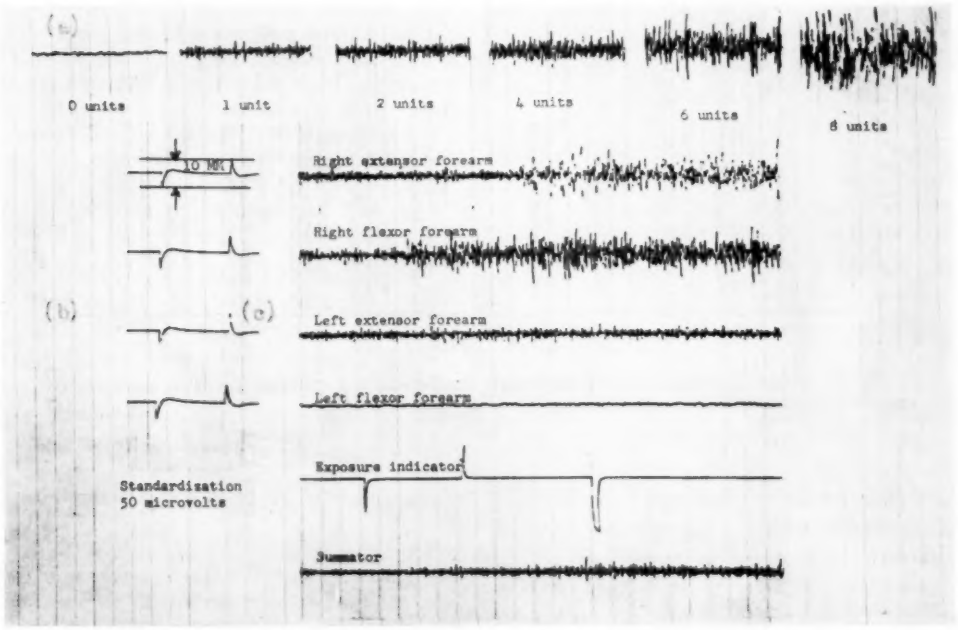

Fig. 1.—Composite record illustrating (*a*) muscle tension, as recorded in units, from 0 to 8; (*b*) standardization of amplification, a 50-mv. signal producing a 10-mm. deflection; (*c*) a section of a recording showing the muscle tension in, from top to bottom, right extensor forearm, right flexor forearm, left extensor forearm, and left flexor forearm. The fifth channel indicates the tachistoscopic exposure. The first and second deflections are associated with an alerting signal. The third deflection is related to the exposure time of the stimulus. The sixth channel shows the average of the muscle tension in the four leads; i. e., it adds the tension in the four leads and divides by 4.

Twelve stimulus words (Fig. 2) were presented visually by means of the tachistoscope. Eight four- and five-letter words were neutral words of equivalent familiarity chosen from the Thorndike Frequency Table.[24] Four words were commonly used emotionally charged words, used by other investigators.¶ Three preliminary words were shown in identical fashion to acquaint the subjects with the

¶ References 3 and 16.

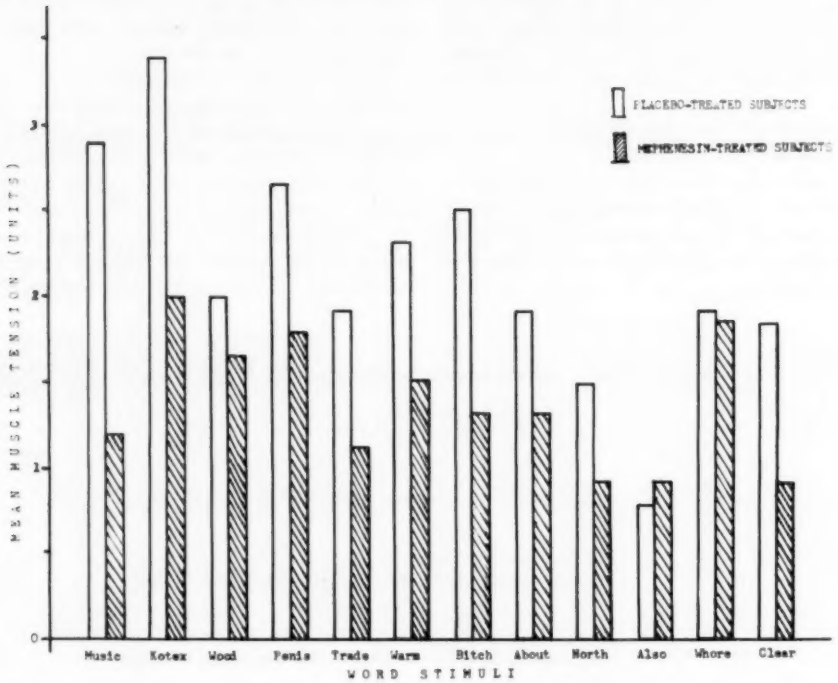

Fig. 2.—Graph illustrating the mean muscle tensions of the stimulus words in the placebo- and the mephenesin-treated subjects.

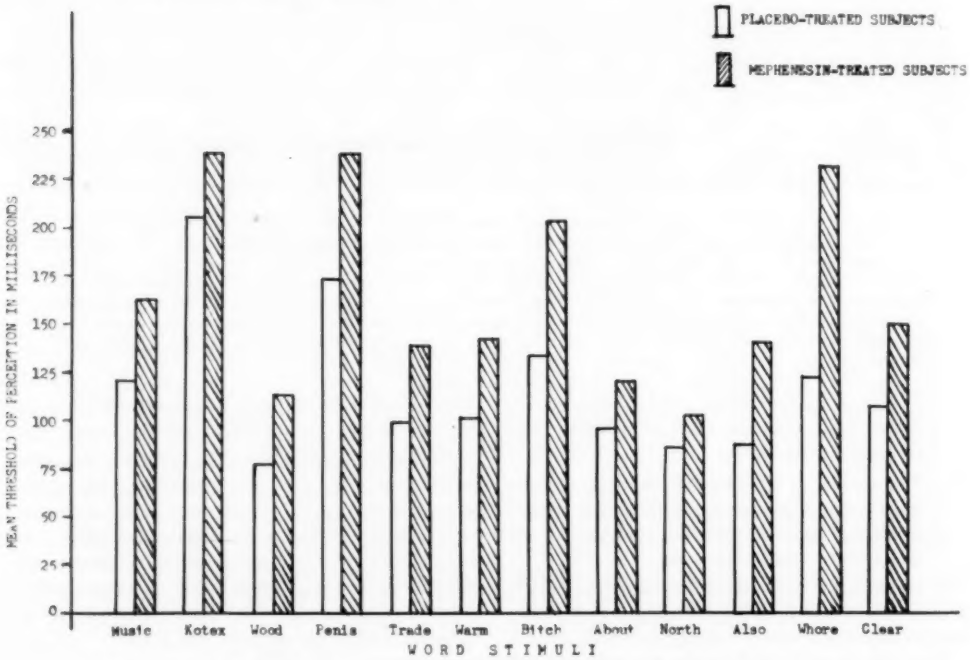

Fig. 3.—Graph illustrating the mean thresholds for correct recognition of the stimulus words in the placebo- and the mephenesin-treated subjects.

procedure and to get the range of each patient's threshold of perception. Exposures were started at 30 msec. during a period of base-line muscle tension and increased at regular intervals until the word was correctly reported.

The subject was seated comfortably in a straight-backed chair with arm rests and a dental headrest for suport. Muscle tension was measured electromyographically with a Grass eight-channel pen recorder standardized so that a 50μv. signal gave a 10 mm. deflection (Fig. 1). The tension in the flexor and extensor muscles of each forearm was recorded. These sites were determined by measurement, as suggested by Davis,[4] and bipolar recordings were made. The resistance of the skin over the selected muscle bundles was reduced below 10 kilohms by cleansing with acetone and rubbing the skin surface with electrode jelly. German-silver-plated brass electrodes 2 cm. in diameter were strapped over the sites with adhesive tape. A preliminary rest period was used to establish a base line of resting muscle tension.

Muscle tension was recorded continuously during tachistoscopic exposures and then either for two minutes after correct report of the word or until tension had returned to near zero. A 30-second rest period was given, and the next stimulus word was shown if tension had returned to the base line. When tension persisted, the rest period was prolonged until one could proceed from a basal level.

The exposure time at the first correct reporting was noted for each word, and the mean muscle tension, from the moment of the first tachistoscopic presentation to the moment of correct reporting, was determined. Muscle tension for each lead was graded in units of 0 to 8 in quasigeometric progression, as is shown in Figure 1. One unit is approximately equal to 12μv.

Calculations of the p values were made for differences in thresholds of perception and differences in muscle tensions for subjects receiving placebo and for subjects receiving mephenesin for all the words and for neutral words and charged words separately, and for the individual word stimuli. Correlation coefficients were calculated for the relationships between thresholds and tensions for the individual subjects on placebo and on mephenesin administration for the two groups separately, and for each word of the stimulus list.

RESULTS

The mephenesin-treated group as compared with the placebo-treated group showed a lower mean muscle tension for the total word list. This is shown in Column 1 of Table 1 and is statistically significant at better than the 0.01 level of confidence. Table 1, Column 3, also illustrates the lower level of mean muscle tension for neutral words in the mephenesin-treated subjects as compared with that for the placebo-treated subjects. This, too, is statistically significant at better than the 0.01 level of confidence. The difference in mean muscle tension for charged words between the mephenesin-treated and the placebo-treated group is shown in Column 2, and is significant at better than the 0.05 level of confidence. Thus, the mephenesin-treated group shows less muscle tension consistently for the total word list, the neutral words, and the charged words, to a significant degree.

TABLE 1.—*Mean Muscle Tensions, in Units, After Placebo and After Mephenesin*

Mean Muscle Tensions, in Units	Total Word List	Charged Words	Neutral Words	C—N	$\frac{C-N}{N}$%	p
After placebo	2.14	2.64	1.88	0.76	40%	<0.05
After mephenesin	1.39	1.75	1.21	0.54	45%	>0.05 (not sig.)
P—M	0.75	0.89	0.67			
$\frac{P-M}{P}$%	35%	34%	36%			
p	<0.01	<0.05	<0.01			

2-6.

Since a secondary object of this procedure was to determine whether emotionally charged words had a greater effect on muscle tension than did neutral words, the means of the muscle tensions of the neutral and charged words were compared. The placebo-treated group revealed 40% less tension for the neutral than for the charged words. This is significant at better than the 0.05 level of confidence (Table 1, Line 1). The mephenesin-treated group showed a much lower mean muscle tension for both charged and neutral words. In fact, for the mephenesin-treated group the mean muscle

TABLE 2.—*Mean Thresholds of Perception, in Milliseconds, for the Stimulus Words After Mephenesin and After Placebo*

Mean Thresholds of Perception, Msec.	Total Word List	Charged Words	Neutral Words	C—N	$\frac{C-N}{N}$%	*p*
After mephenesin	167	229	135	94	70%	<0.01
After placebo	119	161	98	63	64%	<0.01
M—P	48	68	37			
$\frac{M-P}{P}$%	40%	42%	38%			
p	<0.01	<0.05	<0.05			

tension for charged words was lower than the mean muscle tension for the neutral words in the placebo-treated group. Within the mephenesin-treated group the difference in mean muscle tension between neutral and charged words was 0.54 unit, or 45% less tension for the neutral words (Table 1, Line 2). This difference is not statistically significant (Table 1).

Data dealing with the levels of the thresholds of perception are presented in Table 2. The mean threshold of perception of the total word list was 40% higher (Table 2, Column 1) for the mephenesin-treated group than for the placebo-treated group. This difference in threshold is significant at better than the 0.01 level of confidence. Similarly, the mean thresholds of perception for both the charged and the neutral words in the mephenesin-treated group are about 40% higher than the comparable thresholds in the placebo-treated group (Table 2, Columns 2 and 3). This difference is significant at better than the 0.05 level of confidence. Thus, subjects treated with mephenesin show significantly higher thresholds of perception for the total list and for the charged and neutral words.

The differences in the thresholds of perception between neutral and charged words were evaluated for both the placebo- and the mephenesin-treated group. Subjects in the mephenesin-treated group showed a 70% higher threshold of perception for charged than for neutral words (Table 2, Line 1). The control cases showed a 64% increase in threshold of perception for charged as compared with neutral words (Table 2, Line 2). Both these differences are significant at better than the 0.01 level of confidence.

Table 3 shows a comparison of mean tensions for the individual words in subjects receiving the placebo and in subjects receiving mephenesin. There was a lower mean muscle tension in the mephenesin group for 11 of the 12 words. The comparisons are shown graphically in Figure 2. Although no

TABLE 3.—*Mean Muscle Tensions, in Units, of the Individual Stimulus Words After Placebo and Mephenesin Administration*

Mean Muscle Tensions, Units	Music	Kotex	Wood	Penis	Trade	Warm	Bitch	About	North	Also	Whore	Clear
Placebo	2.90	3.40	2.00	2.66	1.93	2.33	2.53	1.93	1.50	0.79	1.93	1.86
Mephenesin	1.20	2.00	1.66	1.80	1.13	1.53	1.33	1.33	0.93	0.93	1.87	0.93
P—M	1.70	1.40	0.34	0.86	0.80	1.12	1.12	0.60	0.57	—0.14	0.06	0.93
$\frac{P-M}{P}$%	58%	41%	17%	32%	41%	47%	47%	31%	38%	—17%	3%	50%

TABLE 4.—*Mean Thresholds of Perception, in Milliseconds, for the Individual Stimulus Words After Mephenesin and After Placebo Administration*

Mean Thresholds of Perception, Msec.	Music	Kotex	Wood	Penis	Trade	Warm	Bitch	About	North	Also	Whore	Clear
Mephenesin	163	240	114	239	140	144	205	122	104	142	233	151
Placebo	121	207	79	175	100	101	135	97	87	89	124	109
M—P	42	33	35	64	40	43	70	25	17	53	109	42
$\frac{M-P}{P}$%	34%	15%	44%	36%	40%	42%	51%	25%	19%	59%	87%	38%

TABLE 5.—*Rank Order Differences in Mean Muscle Tensions and Mean Thresholds of Perception for Subjects Receiving Placebo* *

A. Decreasing Order of Absolute Differences in Mean Muscle Tensions				B. Decreasing Order of Percentage Differences in Mean Thresholds of Perception			
	Tensions, Units				Thresholds, Msec.		
Case No.	N	C	C—N	Case No.	N	C	$\frac{C-N}{N}$ %
12	3.00	6.00	3.00	12	88	240	173
13	1.50	3.75	2.25	15	58	128	121
10	1.50	3.50	2.00	16	69	135	96
4	1.87	3.75	1.88	4	94	170	81
16	2.75	4.00	1.25	22	184	333	81
5	1.37	2.50	1.13	5	74	115	59
23	0.13	0.75	0.62	13	65	100	54
8	1.25	1.75	0.50	29	71	105	48
15	3.75	4.25	0.50	28	49	70	43
20	1.88	2.25	0.37	19	115	160	39
29	0.00	0.25	0.25	10	98	130	32
19	1.50	1.00	—0.50	20	67	85	29
22	4.00	3.33	—0.67	23	89	110	24
14	2.50	1.75	—0.75	14	100	88	—12
28	2.00	1.00	—1.00	8	288	244	—15

* N indicates neutral words; C, charged words.

single word showed a statistically significant difference in tension for the mephenesin as contrasted with the placebo group, the overall difference for the entire word list is statistically significant, as shown in Table 1, Columns 1, 2, and 3.

Comparison of the mean thresholds of perception for the individual words in the mephenesin- and placebo-treated subjects is shown in Table 4. All 12 words show higher thresholds for subjects receiving mephenesin, and this is graphically shown in Figure 3. Again, no statistically significant difference between the two groups can be shown for any single word, but for the entire word list the difference is statistically significant (Table 2, Columns 1, 2, and 3).

Correlations between mean muscle tensions and mean thresholds of perception were computed for the list of 12 words. The coefficients of correlation were determined from the data in Tables 3 and 4. The thresholds of perception and muscle tension of the subjects treated with the placebo showed

TABLE 6.—*Rank Order Differences in Mean Muscle Tensions and Mean Thresholds of Perception for Subjects Receiving Mephenesin* *

Decreasing Order of Absolute Difference in Mean Muscle Tensions				Decreasing Order of Percentage Difference in Mean Thresholds of Perception			
	Tensions, Units				Thresholds, Msec.		
Case No.	C	N	C—N	Case No.	C	N	$\frac{C-N}{N}$ %
27	4.75	1.75	3.00	17	288	98	194
7	5.75	3.87	1.88	26	688	268	157
26	3.75	2.00	1.75	27	90	39	130
11	1.50	0.50	1.00	21	588	306	87
9	1.25	0.37	0.88	24	313	185	80
24	1.00	0.50	0.50	11	563	384	47
21	2.00	1.62	0.38	9	255	179	42
17	0.75	0.50	0.25	1	73	56	29
30	1.25	1.50	0.25	31	63	49	29
1	0.50	0.37	0.13	7	50	40	25
31	0.50	0.37	0.13	18	110	89	24
2	0.00	0.00	0.00	30	173	148	17
18	1.50	1.50	0.00	2	80	71	13
6	0.00	0.57	—0.57	6	60	53	13
3	1.50	2.87	—1.37	3	50	50	0

* C indicates charged words; N, neutral words.

a coefficient of correlation of 0.94, while for the mephenesin-treated group the coefficient of correlation was 0.97. These values are statistically significant at better than the 0.01 level of confidence.

The individual subjects in the placebo group are listed in Table 5, in order of the differences in responses to charged and neutral words. Table 5A represents the differences in mean muscle tension. Table 5B represents the differences in mean thresholds of perception between charged and neutral words. A and B of Table 5 were compared to see whether a significant correlation exists. The coefficient of correlation was found to be 0.67, which is significant at better than the 0.01 level of confidence. The mephenesin-group response levels were ranked and correlated in a similar fashion (Table 6). Again, the coefficient of correlation between thresholds of perception and muscle tensions, of 0.64, is significant at better than the 0.01 level of confidence.

COMMENT

Preliminary experiments showed that it was not possible to test the same subjects on both placebo and mephenesin without making major alterations in the word lists and total procedure, because familiarity altered responses. Thus, each subject could not serve as his own control. However, the use of two similar groups of subjects does permit group comparisons, and this method was applied to the study of mephenesin, with statistically significant results.

Mephenesin-treated subjects showed about 35% less muscle tension than placebo-treated subjects. This difference held for neutral and charged words, as well as for the total word list. At the same time, thresholds of perception were about 40% higher in the mephenesin-treated subjects. Neutral and charged words and the total word lists showed approximately the same elevation of threshold. These differences in mean muscle tension and threshold of perception are in opposite directions but of the same order of magnitude.

The effects of mephenesin on muscle tension and thresholds of perception are slightly greater on charged words than on neutral words. Muscle tension is lower and the threshold of perception is higher for the charged than for the neutral words. The effect on muscle tension is of such order that after mephenesin even the charged words have a lower mean tension than do the neutral words in the placebo group (Table 1). Thresholds of perception are not as strikingly affected (Table 2).

These effects of mephenesin on muscle tension support other reports describing mephenesin as a muscle relaxant. The differences in thresholds of perception are equally striking in our experiment. No previous reports describe such an action, although visual disturbances are mentioned. Any conclusion as to the mode of action producing this effect is not warranted by this study. Possibly both the decrease in muscle tension and the increase in threshold of perception are the result of a sedative effect of mephenesin, whereby many bodily processes are decreased.

The described effects of mephenesin are quite compatible with its reported effects in alcoholic patients, that is, decrease in tremor and anxiety and a slightly sedative action.

It should be noted that the dose used in this study was rather large, 3.0 gm. A previous trial with a 1.0 gram dose showed little effect on muscle tension.

Toxic effects were not clear-cut. Two subjects on mephenesin treatment complained of lightheadedness, nausea, blurring of vision, and sleepiness. Notably, one subject had similar symptoms after receiving placebo. In this study, it was impossible to evaluate the side-effects of mephenesin.

Earlier studies on thresholds of perception revealed significant increases in thresholds for charged words as compared with neutral words. A similar technique in the current experiment gives evidence that muscle tension, likewise, is significantly greater for charged- than for neutral-word stimuli.

SUMMARY AND CONCLUSION

A technique is presented for experimental evaluation of a drug in human subjects by inducing and measuring muscle tension.

Mephenesin decreases the muscle tension associated with recognizing neutral and emotionally charged stimulus words.

The thresholds of perception of words, neutral and emotionally charged, are elevated when mephenesin (3.0 gm.) is administered.

The group of neutral words induces less muscle tension than does the group of charged words.

Similarly, the group of neutral words is recognized at lower thresholds of perception than is the group of charged words.

This study was conducted under a grant extended to us by E. R. Squibb & Sons; they also supplied the mephenesin, under their brand name Tolserol, and the placebos for this series.

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Presenile Dementia of the Jakob Type

Corticostriospinal Degeneration

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The term presenile dementia is generally applied to "primary" psychoses occurring in the presenium and characterized by intellectual deterioration structural ("organic") in type. The causation of these diseases is unknown. However, because of the age of the patients, it is usually assumed that senescence plays some, still obscure, etiologic role.[1] Two broad groups of presenile dementias may be recognized: The first includes Alzheimer's and Pick's disease, two well-established clinicopathological entities; the second comprises a small number of still ill-defined conditions variously associated with names of investigators, such as Jakob,* Creutzfeldt,[4] Heidenhain,[5] Kraepelin,[6] and others. Curiously enough, the latter group has received scanty attention in the American literature; the purpose of this presentation is to contribute to its study by reporting and discussing the clinical and pathologic findings of two cases. Pertinent clinical and pathological data on similar patients published in the literature were evaluated in the attempt to characterize better these cases, which occur perhaps more frequently than is commonly believed.

REPORT OF CASES

CASE 1.—A 59-year-old man was admitted to Veterans Administration Hospital, Montrose, N. Y., on Jan. 7, 1954, because of psychotic manifestations and "bulbar palsy." Significant data in the family history were that a sister was a patient in a state hospital (diagnosis, alcoholic psychosis) and the mother had died in old age while in a state of dementia, which was diagnosed as arteriosclerotic in nature. Two sisters and three brothers were living and well. The patient's past history was negative for any serious disease. He was a carpenter by trade, unreliable in his work, a poor provider, erratic in behavior, and prone to alcoholic excesses. In December, 1952, at the age of 58, it was noted that the patient was unable to concentrate, became forgetful, and appeared preoccupied. Shortly after, he experienced difficulty in swallowing food and in talking. Within a few months, he became disoriented, confused, depressed, and unable to speak. On Nov. 18, 1953, he was admitted to Hudson State Hospital, where there was noted weakness of the arms, atrophy and fibrillation of the interosseus muscles, increased deep reflexes, an inconstant left Babinski sign, inability to talk and swallow, and atrophy and fibrillation of the tongue. Mentally, the patient was confused; disoriented for time, places, and persons, and depressed in mood, and had frequent attacks of explosive laughter and crying. During two months' hospitalization, there was considerable weight loss in spite of a high-caloric, high-vitamin diet. The diagnosis upon transfer to the Veterans Administration Hospital was "psychosis with other diseases of the nervous system: amyotrophic lateral sclerosis."

On admission, the patient was markedly dehydrated and in very poor nutritional condition. There was radiological evidence of aspiration pneumonitis at the right base. The systemic examination was otherwise negative. The blood pressure was 120/80, and there was no evidence of peripheral vascular disease. Routine laboratory studies were essentially negative. Neurologically, there was atrophy of all extremities, with increased deep reflexes, sluggish abdominal skin reflexes, and a left Babinski sign. Fibrillations of the tongue and of the muscles of the shoulder girdle were present. The patient was unable to swallow and was constantly drooling. Speech was limited to an incomprehensible muttering. The patient appeared disoriented and confused. Gastrostomy for feeding purposes was performed one month after admission. The course was rapidly downhill, and death occurred April 12,

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From the Veterans Administration Hospital (Dr. Bornstein, Chief of Laboratory Service; Dr. Jervis, attending neuropathologist).

* References 2 and 3.

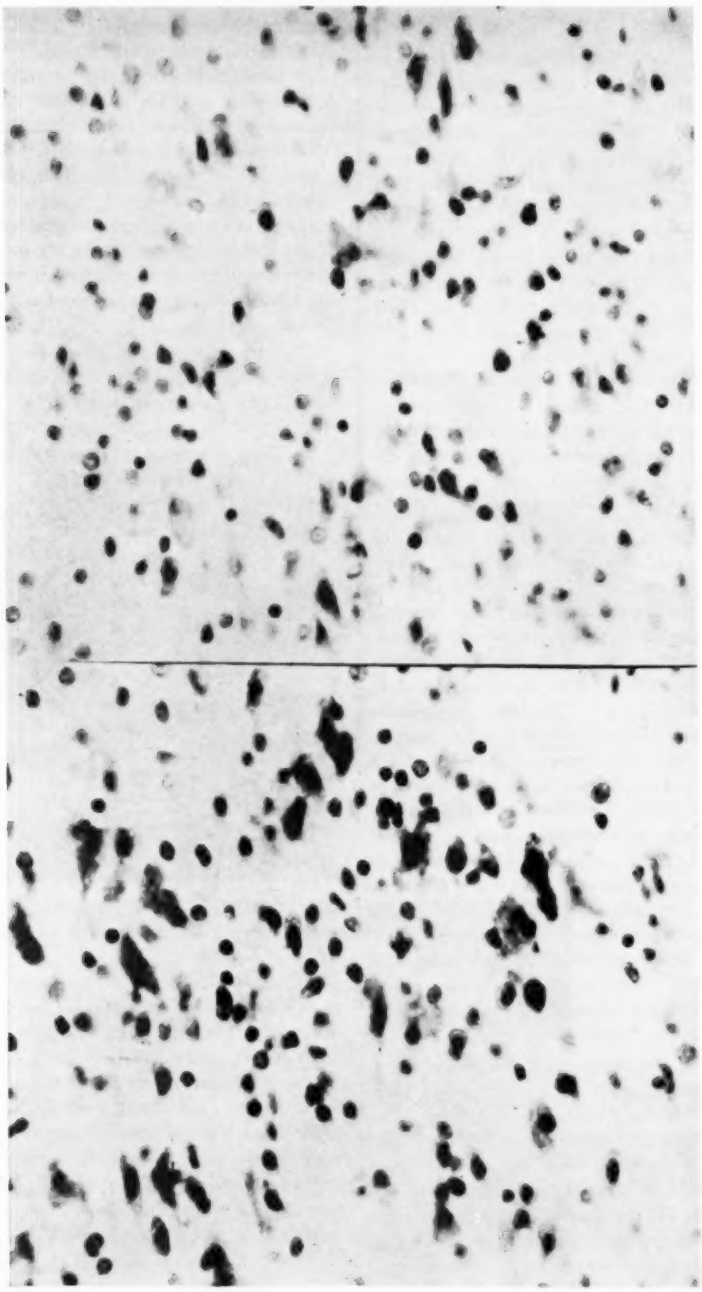

Fig. 1 (Case 1).—Third cellular layer of frontal cortex. Nissl stain; medium power. Upper: "Dropping out" of neurons and proliferation of glia nuclei. Lower: Severe degeneration of neurons and increase of glia nuclei.

1954, three months after admission, following aspiration pneumonitis. The disease had lasted some 16 months.

The autopsy findings outside the central nervous system were irrelevant. The brain weighed 1200 gm. On external inspection, the cerebral cortex appeared moderately atrophic throughout. There was no gross evidence of arteriosclerotic lesions. On histological examination of the cerebral cortex with the Nissl method, a large number of neuron cells showed lesions characterized by distortion of the cell outline, absence of Nissl bodies, pyknosis, and eccentricity of nucleus (Fig. 1). With fat stains, these cells appeared to be replete with granules, which stained red with Sudan III and Sudan IV (scarlet red) and black with Sudan black; they were only partially soluble in the usual fat solvents (acetone, ether, chloroform, and xylene). There were no senile plaques or Alzheimer fibrillary changes in the numerous cortical regions examined, including the hippocampus, a region which is usually considered a selective location for senile changes.

Wide variations in the distribution of nerve cell lesions were found from area to area and, within the same area, from layer to layer. No constant pattern could be established: In some cortical regions, considerable distortion of normal cellular architecture had taken place because of destruction of cells, extending either to the whole cortex or to circumscribed areas (Fig. 1). In other regions, the normal lamination was still recognizable, changes being limited to individual cells. In the deep layers of the cortex increased satellitosis and, less frequently, neuronophagia were present. With Cajal's method an increase in astrocytes could be demonstrated throughout the cortex. This, however, was spotty in distribution. Hypertrophic forms of astrogliocytes were frequently observed. The microglia showed no significant changes, but impregnation was somewhat defective technically. No inflammatory vascular lesions were noted, nor was there histological evidence of arteriosclerotic changes in the cortical vessels.

The myelin in the centrum semiovale appeared intact. Blood vessels were often surrounded by a cuffing of fat-laden scavenger cells, but no true demyelination could be demonstrated. The striatum was somewhat reduced in size, and in the Nissl preparation almost all large cells showed severe degeneration (Fig. 2), the shape being distorted, the size reduced, the cytoplasm laden with fatty pigment, and the nucleus irregular in contour and pyknotic. Neuronophagia was a frequent finding (Fig. 3). The small cells were better preserved. Neuroglia cells were somewhat increased in number and size. A few "simple" senile plaques were present in the striatum (Fig. 4). In the pallidum, the large cells were degenerated. There were no abnormal deposits of pigment or calcium. The cellular picture of the thalamus was similar to that of the cortex. The substantia nigra contained much extracellular black-green pigment; the nerve cells were partly degenerated. In the colliculi, there was considerable decrease in number of neuron cells, increase of glia, and neuronophagia. Red nucleus cells were similarly involved, although to a less severe degree. In the cerebellum, many Purkinje cells had disappeared, and the remaining ones were distorted in shape; Bergmann glia was proliferated. There was no lesion of the white matter. The cells of the dentate nucleus appeared irregularly swollen and filled with fatty material and exhibited eccentric nuclei.

The pons was of normal size, and the nerve cells of the pontine nuclei were little involved. Gliosis of the inferior olivary nuclei was observed in Holzer preparations. Remarkable were the large cells of the hypoglossal nucleus because of their decreased number, distention of the cytoplasm, absence of Nissl bodies, and eccentricity of the nucleus (Fig. 5). Similar lesions were found in the anterior horn of the spinal cord throughout. In myelin preparations there was no degeneration of the pyramidal tract or other spinal tracts; however, in the medulla and upper spinal cord the myelin of the pyramidal fibers stained somewhat paler than normal. There was no gliosis.

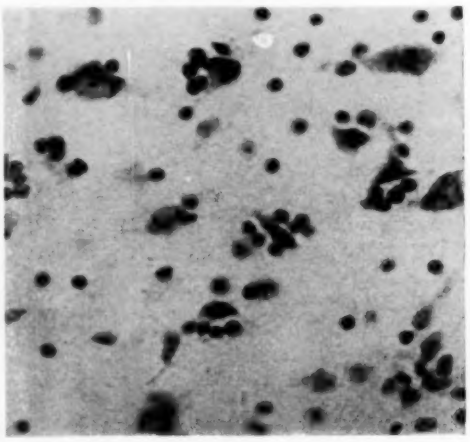

Fig. 2 (Case 1).—Caudatum. Nissl stain; medium power. Severe degeneration of neuron cells.

CASE 2.—A telephone executive, aged 46, was admitted to the Montrose Veterans Administration Hospital in March, 1954, because of "increasing mental confusion," of six months' duration. The family history was negative. The mother and two siblings were living and well. The father had died of heart disease. There were no previous mental

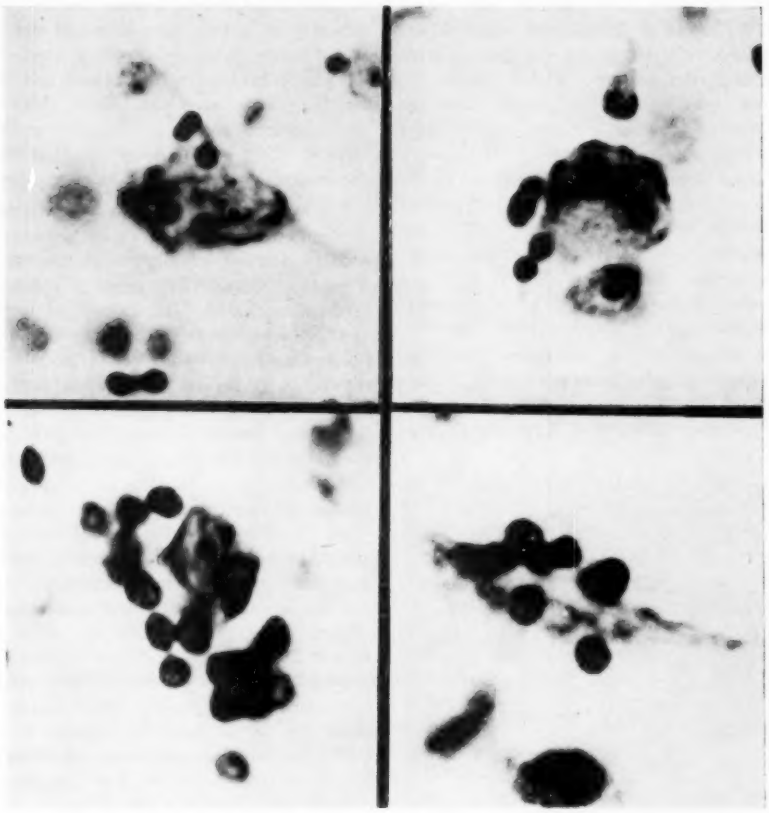

Fig. 3 (Case 1).—Putamen and pallidum. Nissl stain; high power. Various types of degeneration of large neuron cells.

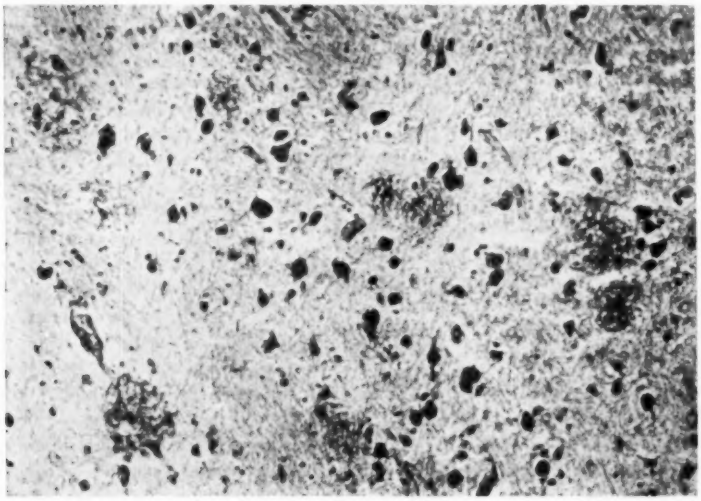

Fig. 4 (Case 1).—Striatum. Von Braunmühl stain; medium power Senile plaques.

disorders in the history of the patient, who was a quiet, reserved, highly intelligent, well-adjusted person. The first manifestations of the disease were impairment of recent memory, apathy, fatigability, and occasional brief episodes of spatial disorientation. The mental condition became rapidly more serious, and three months later confusion was noted, and some vague delusions, the patient believing he was back in military service. Shortly afterward, he became impotent and developed delusions of infidelity. Physical examination was essentially negative. On admission, the patient showed defect of recent memory, some disorientation as to place, poor insight, and marked impairment of judgment. There were no special preoccupations, obsessions, or hallucinations. Routine laboratory tests, including spinal fluid examination, were not remarkable. The blood pressure was 108/74. A ventriculogram

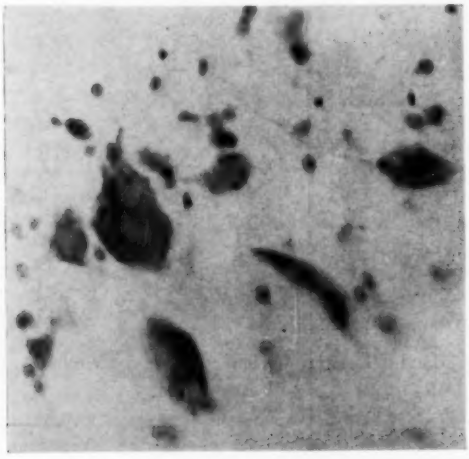

Fig. 5 (Case 1).—Nucleus of 12th nerve. Nissl stain; high power. Degeneration of motor neurons.

revealed considerable bilateral, symmetric ventricular enlargement. Cortical biopsy, performed in another hospital, showed "marked degeneration of neuron cells with atrophy and shrinkage of cellular bodies and tortuosities of dendrites." The EEG disclosed a disorganized pattern of medium and low voltage. The conclusion of the psychologist, based on a battery of tests, was as follows: "The patient is undergoing a deteriorative process resulting in marked reduction of intellectual functioning and social judgment. Memory and learning are particularly affected. There is evidence of confusion, perseveration, and a marked inability to abstract concepts and to shift from one concept to another."

In the hospital, he became restless, depressed, and progressively more disoriented and confused. Bilateral twitching of the arms and legs was observed on several occasions. During the last two months difficulty in swallowing was noted and there were fine tremors of the outstretched hand. Mental deterioration became more profound and the gait unsteady. There was progressive deterioration of speech, which became almost incomprehensible. In October, 1954, some 14 months after the onset of the disease, the patient died, of bronchopneumonia.

The brain weighed 1300 gm. On external examination mild, diffuse cortical atrophy was noted. Cross sections showed grossly no significant deviations from the normal. Histological examination of the cerebral cortex disclosed widespread decrease in the number of neuron cells, resulting in marked alterations of normal cellular architecture. In the orbital region, where the lesions were most pronounced, the cortex was considerably reduced in thickness, neuron cells were few in number, disorderly in arrangement, distorted in shape, usually sclerotic, and exhibited pyknotic nuclei (Fig. 6). Considerable hypertrophy and hyperplasia of the macroglia were noted (Fig. 7). The microglia showed little activity. In silver preparations no senile plaques were noted, nor were there any Alzheimer neurofibrillary changes. No cytoplasmic argentophilic inclusions were observed. In sections stained for fatty substances, almost every nerve cell was replete with lipid granules, which were only partially soluble in the common organic solvents. There was no fatty material free in the tissue or collected in scavenging cells. The blood vessels appeared normal. Marked satellitosis was noted in the deep layers of the cortex. The cortical myelin sheaths were markedly reduced in number and stained palely with hematoxylin. Cortical lesions, similar in type but of less severity than those observed in the orbital cortex, were noted throughout the cortex. Next to the orbital region some frontal convolutions appeared mostly involved. Severe lesions were present also in the temporal regions, although less evenly distributed. In the occipital lobe alterations were scattered, and the parietal regions appeared to be less involved. The distribution was, however, asystematic and capricious in character. The white matter of the hemisphere, which was studied in large coronal sections, stained with the Weil, Herxheimer, and Holzer methods, showed no relevant alterations. Perivascular accumulation of fat-laden cells was occasionally present, and in some regions the myelin was palely stained but no areas of demyelination were noted. There was no histological evidence of arteriosclerotic disease. In the striatum, the large nerve cells were distorted and degenerated, the small cells being better preserved. Nerve cells of the various thalamic nuclei were severely affected, various types and pigmentary infiltration being present (Fig. 8). Increase of glia nuclei was noted throughout the thalamus. In the subthalamic bodies,

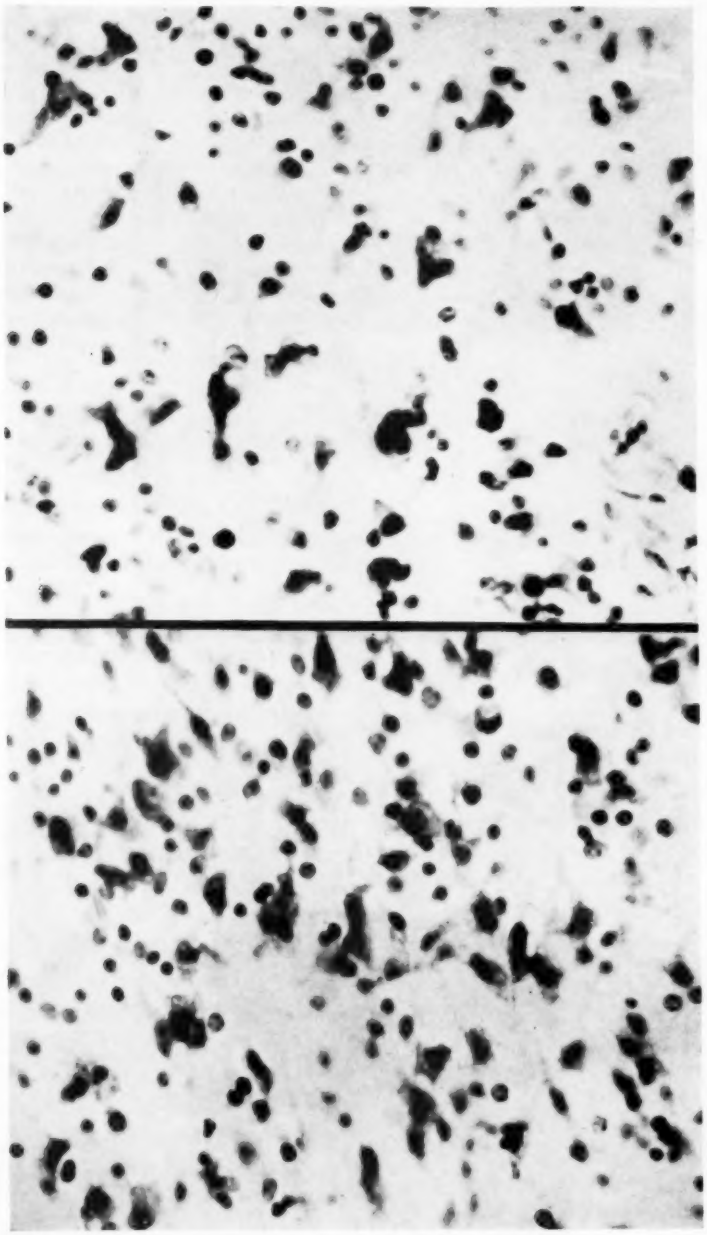

Fig. 6 (Case 2).—Pyramidal layer of the orbital cortex. Nissl stain; medium power. Upper: Scarcity of neurons; severe sclerosis of nerve cells; increase in glia. Lower: Severe degenerative changes of neurons, increase in glia.

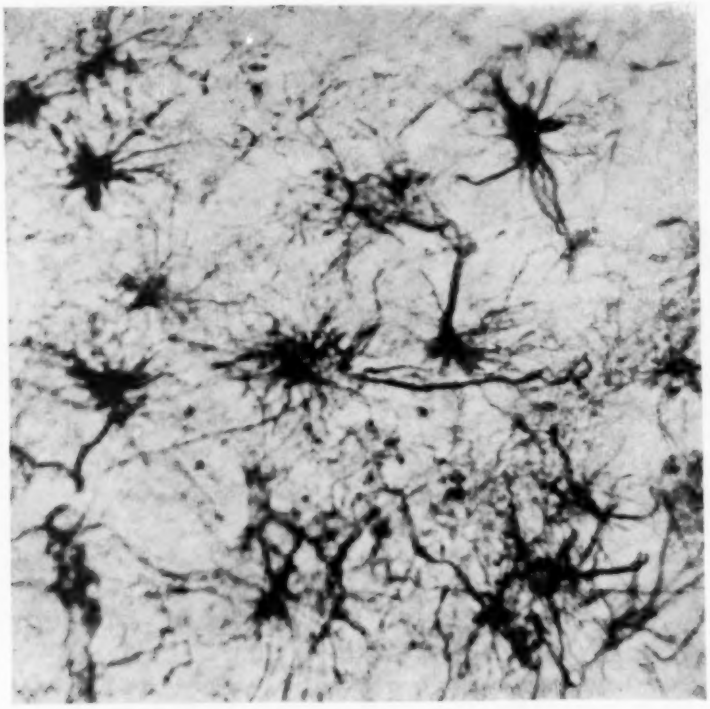

Fig. 7 (Case 2).—Frontal cortex. Cajal stain; high power. Hyperplasia and hypertrophy of macroglia.

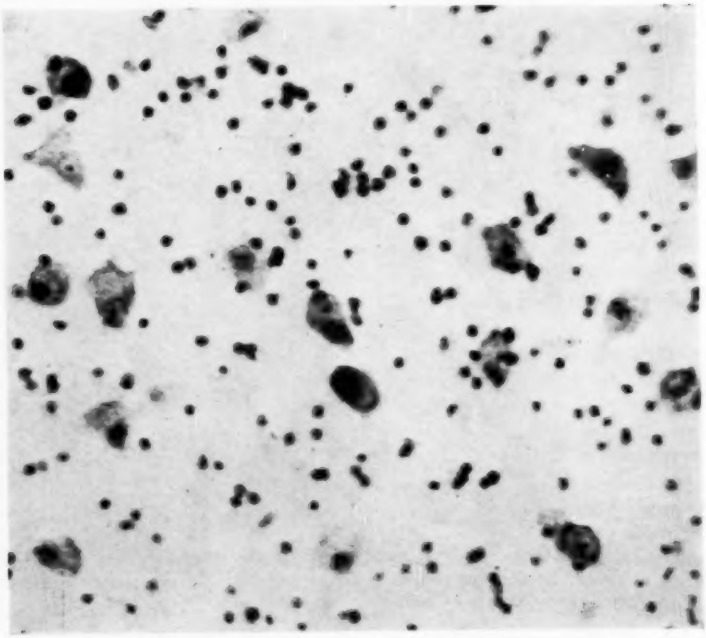

Fig. 8 (Case 2).—Thalamus. Nissl stain; middle power. Degeneration of neurons and increase of glia nuclei.

the nerve cells were swollen and distorted and contained much pigment. The cells of the red nuclei and the substantia nigra were better preserved. Lesions in the cerebellum were mild, consisting essentially of decrease in number of Purkinje cells and proliferation of Bergmann glia. In the pons and medulla, swelling and chromatolysis of cells and eccentric nuclei were a common finding; severe degenerative changes and pyknosis of nuclei were rare. Myelin preparations of these structures were essentially normal. Many large neuron cells of the anterior horn of the spinal cord were distorted in shape, infiltrated with lipid material, and devoid of Nissl bodies. The main fasciculi of the spinal cord showed no demyelination.

COMMENT

The two patients whose cases are here presented showed similar mental manifestations and dissimilar neurological symptoms. The age of onset, 57 and 46 years, respectively, was clearly within the presenile age period. Mental features in both cases were those of a psychosis usually associated with structural changes of the brain, confusion, disorientation, marked memory impairment, and intellectual deficit being in the foreground. Mental deterioration was progressive, without remission, in both cases, and intellectual dilapidation was present in the terminal stage. The course of the disease was relatively rapid, being 16 and 14 months, respectively. On the other hand, in Case 1 the neurological picture was so outstanding and of such a nature as to justify the diagnosis of amyotrophic lateral sclerosis, whereas in Case 2 neurological manifestations were limited to occasional muscular twitchings, dysarthria, some tremors, and terminal inability to swallow.

In contrast to the richness and variety of the clinical picture, the pathological lesions were uniform and rather meager, consisting essentially of widespread degenerative lesions of the neurons with concomitant neuroglia reaction. The morphologic changes were similar in type in the two cases, differing somewhat in distribution, the cortex and thalamus bearing the brunt of the lesions in Case 2, whereas in Case 1 the spinal cord and medulla were more severely involved. Conspicuous by their absence in the cerebral cortex of both cases were the pathological "marks" of senile brains, i. e., senile plaques and Alzheimer's neurofibrillary changes. In addition, grossly, no localized cortical atrophy and, histologically, no myelin or neurocellular changes characteristic of Pick's disease were noted. Finally, there were no arteriosclerotic changes in the blood vessels. It is clear that the cases here described belong into the group of "primary" presenile dementia. Furthermore, on pathological grounds, the diagnosis of Alzheimer's or Pick's disease may be ruled out without difficulty.

The findings may now be compared with those previously reported in cases variously diagnosed as Jakob, Creutzfeldt, Heidenhain, or Kraepelin disease.

The main clinical features of histologically confirmed cases of Jakob-Creutzfeldt disease are summarized in the accompanying Table. It may be seen that the disease affects persons of both sexes, mostly during the fifth and sixth decades of life, but not infrequently in the fourth decade. Conspicuous by his young age is the patient described by Creutzfeldt.[4] The course of the disease is relatively rapid, from a few months to 2 years (average 18 months). Notable exceptions are the case described by Dimitri and Aranovich [18] and those two by Davison and Rabiner,[15] which, however, are somewhat atypical from a clinical point of view. In every instance, with the exception of the last three, dementia was the main feature of the mental picture. The psychosis is of the type usually associated with structural lesion of the brain, and is characterized by memory defect, apathy, and intellectual deterioration. Interesting is one of the cases reported by Jakob,† in which Korsakoff's type of dementia developed, and that by Rauch [19] and Bronisch,[20] exhibiting euphoria and delusions of grandeur. In the terminal stage dementia is usually profound in degree. Speech defect, varying in degree from slight dysarthria to complete dilapidation, is pres-

† References 2 and 3.

Clinical Manifestations of Jakob-Creutzfeldt Disease

Author	Sex	Age at Death	Duration, Mo.	Dementia	Speech Defect	Extra-pyramidal Signs	Amyotrophy	Spasticity Paralysis	Other Signs
Jakob *	F	54	15	+	+	+	−	+	Bulbar signs
	F	34	6	+	±	−	−	+	Schizophrenia-like psychosis
	M	42	12	+	+	−	+	+	Korsakoff's psychosis
	F	39	14	+	+	+	−	+	Paranoid trends
Creutzfeldt [4]	F	23	12	+	+	+	−	+	.....
Kirschbaum [7]	M	44	9	+	+	±	−	−	.....
	M	54	30	+	+	+	−	−	Convulsions
Zimmermann [8]	M	34	24	+	+	−	−	−	Depression
Meyer [9]	M	55	9	+	+	−	+	+	.....
Meggendorfer [10]	F	46	6	+	+	+	−	+	.....
Stender [11]	F	44	15	+	−	−	−	±	Auditory hallucinations
.....	M	21	7	+	−	±	−	(±)	Catatonia
Teichmann [12]	M	44	12	+	+	−	+	+	Depression
Jansen and Monrad-Krohn [13]	M	43	18	+	+	−	−	+	.....
Davison [14]	M	32	18	+	+	+	+	+	.....
	F	50	18	(±)	+	+	−	+	.....
Davison and Rabiner [15]	F	41	24	(±)	−	+	±	+	.....
	F	53	62	(±)	−	+	+	+	.....
McMenemey and Pollak [16]	F	60	5	+	+	−	−	−	.....
Jervis et al.[17]	M	43	12	+	+	−	+	+	.....
Dimitri and Aranovich [18]	M	57	80 (?)	±	−	+	−	±	.....
Rauch and Bronish †	M	44	10	+	+	±	−	−	Dementia-paralytica-like psychosis
Fattovich [21]	F	65	4	+	+	−	±	±	.....
Jacob et al.[22]	M	44	12	+	+	+	−	−	.....
	F	39	9	+	+	+	−	−	Korsakoff's psychosis
Ajuriaguerra et al.[23]	M	38	17	+	+	+	−	+	Arterial hypertension
Heidenhain [24]	M	55	4	+	+	−	−	±	Blindness
	M	53	4	+	+	−	−	±	Blindness
	M	49	72	±	−	+	−	−	.....
Meyer et al.[5]	M	38	6	+	+	−	−	−	.....
Oksala [25]	F	42	12	+	−	+	−	−	Acute catatonia (?)
Gruenthal [6]	F	45	24	+	+	+	−	−	"Catatonic excitement"
Best [26]	M	35	5	+	+	+	−	−	Hallucination
Garçin et al.[27]	F	55	3	+	+	+	−	−	Myoclonus
	F	52	2	(±)	+	+	−	−	.....
Reda and Agostini [28]	M	64	4	+	+	+	−	−	.....
Poursines et al.[29]	M	54	4	+	−	+	−	−	Diplopia; uncoordination

* References 2 and 3.
† References 19 and 20.

ent in almost all cases. It is of considerable diagnostic importance when present in the initial phases of the disease.

Neurological manifestations may be classified under three groups: (1) motor impairment and spasticity of the pyramidal type; (2) extrapyramidal manifestations (rigidity, tremors, athetosis), and (3) localized amyotrophies. As seen in the Table, considerable differences in the incidence of these symptoms and signs are observed from case to case. It should be noted, furthermore, that in several patients listed in the Table as positive, the corresponding manifestations occurred only toward the end of the disease. Finally, the fact should be kept in mind that the demonstration and evaluation of neurological disturbances in extremely demented patients is a matter of considerable difficulty. Some evidence of pyramidal tract disturbance was present in 70% of the reported cases and developed mostly in the terminal stage. Extrapyramidal signs were noted in about half the cases, and in a few patients athetosis, tremors, and rigidity were the outstanding and early complaints. Localized amyotrophy was noted less frequently. In the patients of Teichmann,[12] Meyer,[9] and Jervis and associates,[17] the diagnosis of amyotrophic lateral sclerosis appeared justified on neurological examination.

The clinical picture of Case 1, here reported, is similar in the essential details to the cases reported in the literature of Jakob-Creutzfeldt disease with outstanding neurological manifestations, while Case 2 would fit well into the group of Jakob-Creutzfeldt disease with minor neurological signs.

The pathological findings of published cases of Jakob-Creutzfeldt disease correspond closely to those observed in the present cases. Outstanding lesions are degenerative parenchymatous changes of the cerebral cortex. They vary from acute swelling to sclerosis, pigmentary degeneration, and complete destruction of the neurons. The cortical lesions are irregularly diffuse, with focal accentuation of the process. Concomitant neuroglia reaction is usually present. Thalamic nuclei are involved in a manner similar to that of the cortex. The striatum is usually affected, but the degree of involvement varies considerably from case to case. Even more variable are the lesions in the nuclei of the motor cranial nerves and the anterior horns of the spinal cord; in some instances, as in Case 1 here reported, the spinal lesions are outstanding; in others, as in Case 2, the lesions are minor in degree. The two cases here described, in conclusion, would fit without difficulty within the clinicopathologic syndrome known as Jakob-Creutzfeldt disease.

An attempt has been made to separate from the group of Jakob-Creutzfeldt disease a variety of presenile dementia under the name of Heidenhain's disease.[5] In the Table, the main clinical features of four cases ‡ which might be classified in this group are summarized. The cases of Stender,[11] listed in the Table, could be added. It may be seen that the distinguishing feature is a conspicuous psychotic symptomatology with no or few accompanying neurological signs. Whether these clinical features justify differentiation from the Jakob-Creutzfeldt group is open to doubt. It may readily be seen that Case 2 here described might well be classified as one of Heidenhain's disease. On pathological examination the differentiation between the two conditions is even less sharp. The lesions in the two diseases are similar in type, differing somewhat only in distribution. The occipital cortex is often severely affected. However, the significance of this finding is questionable, since wide variations in distribution of lesions are usually observed from case to case in Jakob-Creutzfeldt disease.

A few additional cases of presenile dementia, similar in some respects to the cases here reported, have been grouped under the term of Kraepelin's disease.[6] As shown in the Table,§ the clinical features are those

‡ References 5 and 24.

§ References 6, 25, and 26.

of a rapidly progressive intellectual deterioration with anxiety, depression, fleeting catatonic states, and speech defect. The course is rapid and the outcome fatal. Pathological changes are characterized by diffuse degenerative changes of the neuron cells, among which so-called "liquefaction" of neurons is outstanding. It is difficult to single out differentiating clinical features from Case 2, here described, and pathological differences may be ascribed only to the "tempo" of the process.

A few cases of presenile dementia have been recently described in which rapid mental deterioration with fatal outcome in a few months was accompanied by neurological signs of the extrapyramidal type, as shown in the Table.‖ Neurocellular lesions of degenerative nature were present in the striatum, thalamus, and, to a less conspicuous degree, in the cerebral cortex. Although the extrapyramidal symptomatology stands out conspicuously, it is clear from the description of these patients that there are close clinical and pathological similarities with the other conditions here discussed.

Summing up, all cases mentioned in this discussion have in common the following features: onset usually in the presenile age; rapid, progressive course; fatal outcome; "organic" dementia; neurological manifestations, and diffuse degenerative lesions of the neuron cells, varying in distribution and relative severity. These common features appear to justify the grouping of all cases into a distinct clinicopathological syndrome. The confusing eponymic terminology might be simplified by substituting for the names of authors the term "corticostriospinal degeneration," first suggested by Wilson,[31] which indicates clearly the localization and nature of the pathological process. Should subgrouping of the syndrome become advisable, the following subdivision is suggested:

1. Spinalstriocortical degeneration. This would include the few cases with a prevalently spinal symptomology, simulating the clinical picture of amyotrophic lateral sclerosis. The patients reported by Meyer,[9] Teichmann,[12] Jervis and associates,[17] and Case 1 here described are instances of this variety.

2. Striocorticalspinal degeneration. The symptomatology is dominantly extrapyramidal, and conspicuous cellular changes are present in the striatum. Examples are the patients of Davison and Rabiner.[15] The case reported by Garçin and associates,[27] Poursines and associates,[29] and Reda [28] may be here included.

3. Corticostriospinal degeneration. This would include all cases presenting as the outstanding manifestation intellectual deterioration and the cortex as the site of prevalent pathological localization. Case 2 and cases of Heidenhain's and Kraepelin's disease may be included in this subgroup.

The etiological factors of the condition are unknown. Genetic factors which play a relevant role in other types of presenile dementias are apparently of little significance. With the notable exception of the extraordinary Backer family, extensively studied by Kirschbaum,[7] Stender,[11] Meggendorfer,[10] and Jacob and associates,[22] and comprising probably 13 affected members, and the family described by Davison and Rabiner,[15] in which the manifestations were somewhat atypical because of the age, the long course, and the mildness of intellectual deterioration, no evidence of genetic mechanism was present in any case reported in the literature. The role of the process of senescence is likewise doubtful, the only element in favor of it being the age of the patient. The type of pathological lesions is not that of senescence. That vitamin depletion may be of some significance has been suggested by similarities between pathological findings in pellagra and in some cases of corticostriospinal degeneration,[30] but no convincing evidence has yet been produced in support of the hypothesis. The type of pathological lesions would suggest the presence of an irreversible toxic process, the nature of which is unknown.

‖ References 27, 28, and 29.

SUMMARY

The clinical and pathological features of two patients affected with a primary form of presenile dementia are described. The first patient, aged 59 years, showed, in addition to intellectual deterioration, neurological symptoms and signs similar to those of amyotrophic lateral sclerosis. In the second patient neurological signs were limited to occasional muscular twitchings, dysarthria, occasional tremors, and terminal inability to swallow. In both patients the mental symptomatology was of the type usually associated with diffuse structural lesions of the brain. The course of the disease, progressive and relatively rapid, was 16 months in the first patient and 14 months in the second. The pathological lesions consisted of widespread degenerative lesions of the neurons with concomitant neuroglia reaction. In the two patients morphologic changes were similar in type; in distribution they differed somewhat, the spinal cord and medulla bearing the brunt of the lesions in Case 1, while in Case 2 the cortex and thalamus were more severely involved.

These findings are compared with those reported in cases of presenile dementias, which have been labeled Jakob's, Creutzfeldt's, Heidenhain's or Kraepelin's disease. Since clinical and pathological features are similar in all these conditions, it is suggested that, in the absence of a better knowledge of etiologic factors, they be grouped into a single clinicopathologic syndrome under the term corticostriospinal degeneration, first proposed by Wilson.

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Excitability of Motoneurones in Acute Experimental Poliomyelitis

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An earlier study from this laboratory (O'Leary, Heinbecker, and Bishop [1]) dealt with correlations between histological and electrophysiological evidences of damage to peripheral axons in experimental poliomyelitis (monkey). The inferences drawn were in accord with the prevalent view that the motoneurone soma is the chief target of the virus. To what extent the damaged somata supplying partially or completely paralyzed extremities can still respond in electrophysiological preparations is debatable. The desire to contribute to the solution of that problem led to the present study.

In the work mentioned above certain monkeys paralyzed for two to three days (Flexner MV strain) were used to stimulate the long motor tracts above the cord segments supplying affected extremities. Such stimulation did not induce perceptible movement, even though the muscles of the same extremities continued to respond to root and nerve stimulation until Wallerian degeneration was becoming evident. In the present, more systematic, approach to the problem motoneurone excitability was gauged by (1) peripheral responses to stimulation of motor cortex, reticular substance, and cord tracts, and (2) alteration in the character of the spinal reflex potential (Lloyd [2]), as recorded from the L 7 ventral root after stimulation of the corresponding L 7 dorsal root. The relevant cord segments for each experiment were sectioned serially and cell counts made to sample the severity and extent of the changes in the motoneurone population.

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METHOD

Macaca mulatta monkeys were used. Except for eight controls, each was injected intracerebrally with a 10% emulsion of the Lansing prototype strain of virus and watched thereafter for the appearance of preparalytic symptoms (Bodian [3]) and for the onset of paralysis. Two of the injected animals were used in the preparalytic phase; the remainder (20), in the first 48 hours after the onset of paralysis. Thiamylal (Surital), courtesy of Parke, Davis & Co., given intravenously or intraperitoneally, was the anesthetic used. Before induction of anesthesia each monkey was examined for alterations in the deep reflexes and for estimation of the degree and distribution of paralysis in the affected parts. Observations were also made upon respiration. After anesthesia a tracheal cannula was inserted. When necessary artificial respiration was maintained throughout the course of an experiment.

Those animals used for motor cortex stimulation and electromyographic recording (three control and nine infected animals) were strapped into a special chair. The skull was fixed in a suspensory frame attached to an upright projecting from the chair back. Both motor cortices were then exposed and pairs of needle electrodes thrust into selected muscles of each extremity. Electromyographic (EMG) recording was done routinely from the tibialis anterior, gastrocnemius-soleus, and quadriceps muscles of each lower extremity and from the biceps, triceps, and brachioradialis of each upper extremity. Other muscles were also selected, depending upon the pattern of movement evident in the particular experiment. Ordinarily left and right corresponding pairs of muscle leads from the lower (and later from the upper) extremity musculature were led into alternate channels of a six-channel electroencephalograph. The leg (or arm) areas of

the motor cortices were then explored with bipolar electrodes (60-cycle frequency) to obtain threshold contractions for stimuli 0.01, 0.1, and 1.0 msec. in duration. Histological controls of the motor cortex were studied in each instance. While cortical inflammatory reaction was often in evidence, it did not seem sufficient in degree in any case to affect materially the results presented.

In the other group of experiments (5 control and 13 infected animals) motor cortices, medulla, and lumbosacral cord were all exposed. The spinal roots were then identified, and, after cutting the L 6 and L 7 dorsal roots, electrodes were placed upon each between its cut end and the dorsal root entry zone. The L 7 ventral root was similarly divided, a pair of recording electrodes being placed so that the distal member lay upon the crushed central end of the divided root. In the usual experiment the L 7 dorsal root stimulus was used to evoke a ventral L 7 volley. The L 6 stimulus was used for conditioning that volley. Ordinarily such an L 6 stimulus was set subliminally and applied at intervals of 1 to 40 msec. preceding the dorsal L 7 stimulus to test for interactions contingent upon the overlapping of root collaterals in their distribution to motoneurones.

While the ventral-root-recording electrodes were still in place, contralateral motor cortex and ipsilateral mesial medullary reticular substance were stimulated successively with single shocks, and the root discharges for each were recorded. When there was a difference in the severity of paralysis upon the two sides, the roots of the more affected side were studied first. In certain preparations the posterior tibial and peroneal nerves were stimulated also, records again being obtained from the ventral L 7 root.

All relevant cord segments were sectioned serially at 15μ. In the experiments utilizing motor cortex stimulation and EMG recording the lumbosacral cord was not exposed, and these animals were injected with 15% formalin containing 1% acetic acid. In the experiments in which the lumbosacral cord was exposed, the appropriate segments were dissected free and fixed by suspension in liberal quantities of that fluid. The motoneurone counts were designed to sample the cell population of the ventral gray matter. Both mesial and lateral cell columns were included. Cells under 20μ were excluded. Five or six sections were counted for each segment. At first we tried to classify the degree of damage to each cell in accordance with the plates of Bodian's [3] classic study. Accordingly, we grouped as "mild damage" those that corresponded with *2*, *3*, and *4* of Bodian's Plate I; as "moderate," those like *5*, *6*, *7*, and *8* of that plate, and as "severe," those resembling the cells of Bodian's Plate II. However, three different observers consistently obtained bimodal distributions, counts of cells with "moderate" damage always being low numerically in our material. It seemed to us that this bimodality might relate to the brief period a cell under destruction remained in the "moderate" group, and accordingly we revised our counts to present data only upon Grade-1- (mildly) and Grade-2- (severely) damaged motoneurones for comparison with normals. We recognize that the classification is an arbitrary one, and that completely destroyed motoneurones go uncounted. Other factors, such as differences between strains in the rate of virus multiplication in motoneurones, may also have importance in determining how fast these cells pass from early chromatolysis to complete destruction. Finally, it is emphasized that the pattern of loss in functioning which we seek to establish is applicable only to the virus strain used in the experiments.

OBSERVATIONS

Motor Cortex Stimulation with Electromyographic Recording

The data from infected animals were selected to demonstrate that as paralysis develops (1) it is the least damaged of the motoneurones which convey the threshold responses to cortical activation; (2) internuncial pools continue to function as long as there are sufficient remaining motoneurones to transmit the activated process to the musculature, and (3) even when paralysis is so complete that the muscles can no longer be activated by ordinary cortical stimulation, highly synchronized convulsive discharges set up by strong cortical stimulation may continue to be transmitted through whatever remains of the motoneurone pool.

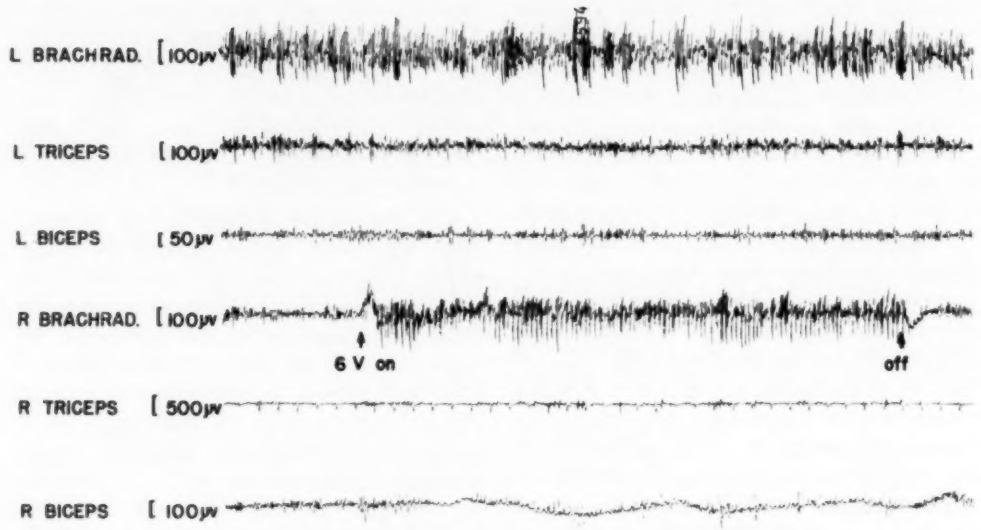
The three control and nine infected monkeys were maintained under light thiamylal anesthesia throughout. In general, our observations upon the controls confirm those of Gellhorn,[4] with respect to the effect both of variation in muscle tone upon the response pattern and of change in posture of the limb. With use of a 60-cycle stimulus frequency, 1-msec. pulse duration, and bipolar electrodes, threshold contraction of the appropriate contralateral musculature, observed visually, was obtained from a zone 5-7 mm. wide, extending forward from the central sulcus; the stimulus strength at

threshold varied between 0.85 and 1.5 volts. At that strength the contralateral response consisted in discrete, sustained movements of the distal parts, appearing either immediately or after a latency of several seconds. At two or three times threshold the contractions quickened perceptibly and the response pattern enlarged to include more proximal muscles. However, even at threshold the movements were composite, involving, for example, feeble adduction of a thumb with separation, and at times flexion, of the other digits, together with minimal flexion or extension of the wrist. Liminal contraction in the distal musculature was often accompanied by EMG alterations in the more proximal muscles. Depending on the cortical point stimulated near threshold, the biceps or triceps of the upper limb, for example, might be activated principally, either reduction in the level of tonic activity or activation, in slighter degree, appearing in the antagonist. Activation of a contralateral muscle might also be accompanied by reduction in the tonic activity of its ipsilateral homologue. Such combinations likely necessitate the operation of cord internuncials to mediate the cortically initiated activity to the motoneurones.

Data from five infected monkeys are presented. For the experiment illustrated in Figure 1, characterized as late preparalytic, the animal when examined just prior to use showed only minimal weakness in the grip of the left hand and absence of the left biceps jerk. On the right side of the cervical cord approximately 20% of the motoneurones over 20μ in size had a normal appearance, the remainder showing Grade 1 change; the left side had no normal cells, 65% showing Grade 1 and 35% Grade 2 change. In spite of these alterations, all muscle pairs recorded showed significant tonic activity; and, using a 3- to 6-volt stimulus, each cortical arm area strongly activated the muscles of the contralateral arm. At one stage of recording, activation of a contralateral brachioradialis was accompanied by reduction in amplitude of the tonic activity of the ipsilateral one. Another animal used in the late preparalytic period had a similar level of tonic activity and showed good activation at 1.5 volts. The distribution of affected motoneurones was similar, although the C 5-C 6 segments had more cells in Grade 2 change; the C 7-C 8 segments more in Grade 1.

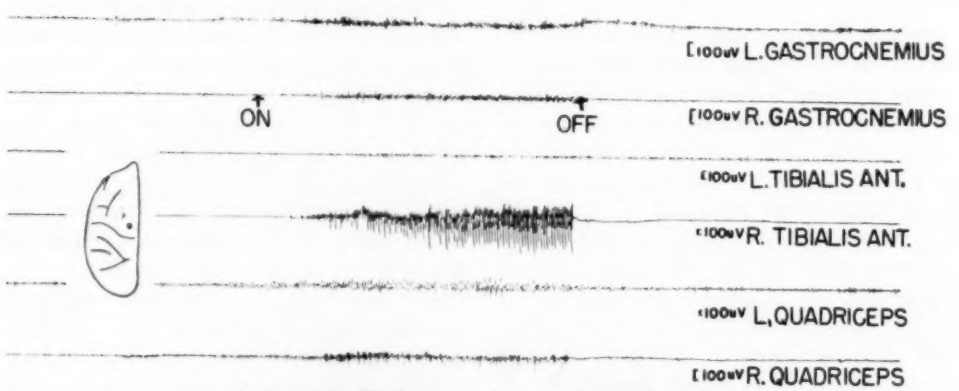
The tracing in Figure 2 was obtained from an animal which became paralyzed slowly. When used at 40 hours, there was 2+ weakness (4+ was graded as complete flaccid paralysis) in all movements of the right leg; 3+ in the left. Histologically, very few normal motoneurones remained. For the right side of the lumbosacral cord Grade-1- and Grade-2- damaged motoneurones occurred in the ratio of 4 : 1. Upon the left side the ratio was 2.5 : 1. Using cortical stimulation at 3 volts, it was possible to activate musculature of either foot and to show activation of thigh and leg muscles by EMG recording. Figure 2 illustrates contralateral activation of the right tibialis anterior from the left motor cortex at 3 volts, with coincident less pronounced bilateral activation of the quadriceps and gastrocnemius muscles. Thus, the stimulus threshold was not markedly elevated in spite of a high incidence of motoneurone damage.

Figure 3 is from an animal that was completely quadriplegic at 48 hours, volitional movements remaining only in the face, neck, and tail. Deep reflexes were absent, and there was significant respiratory involvement. Counts for the cervical segments indicated no remaining normal motoneurones, and a ratio of 1 : 1 existed between the less and the more severely damaged ones. Had it been possible to take into consideration the total of destroyed cells, an inaccuracy inherent in such counts, it is likely that the figure for severely damaged cells would have been still higher. For the lumbosacral cord the situation was similar. In the upper tracing of Figure 3 we believe it important that the cortical stimulus required to activate the left triceps from the right cortex was only 3 volts, and that lessening in tonic activity was evident in the right biceps and triceps during the period



MACAQUE NO. 15 LATE PREPARALYTIC
(LEFT MOTOR CORTEX STIMULATION)

Fig. 1.—EMG recording, preparalytic phase; stimulation of left motor cortex arm area, 60 cycles, 3 volts, 1.0 msec. pulse, light thiamylal anesthesia. Tracings from biceps, triceps, and brachioradialis muscles, those from left and right members of homologous pairs occupying adjoining channels. The tonic activity of the muscles as recorded did not deviate significantly from that of controls. The tracing from the left brachioradialis was recorded at higher sensitivity than that used for the right one in order to detect any change in activity during the stimulatory period. Of the three right-sided muscles, only the brachioradialis was clearly activated from the cortical point used in this trial (6 volts); the tracing shows recruitment of new units during stimulation.



MACAQUE 4-FEB.4'54 40 HOURS PARAL-
YSIS- L.MOTOR CORTEX-R. LEG

Fig. 2.—Paralysis developed slowly, and the experiment was delayed until 40 hours after its onset. At that time there was 2+ weakness in all movements of the right leg and 3+ weakness on the left. Deep reflexes were absent in the legs bilaterally. The threshold for movement in the right leg from activation of the leg area, left motor cortex, was 3 volts, 1.0 msec. pulse, and involved extension of digits 1, 2, and 3. The EMG response reached significantly higher amplitude in the contralateral tibialis anterior. At this time in the experiment quadriceps and gastrocnemii muscles showed minor activation bilaterally; in other trials the tonic activity of the ipsilateral muscles was lessened during stimulation, showing how variable the response pattern may be. Reference to the extent of cell damage is given in the text.

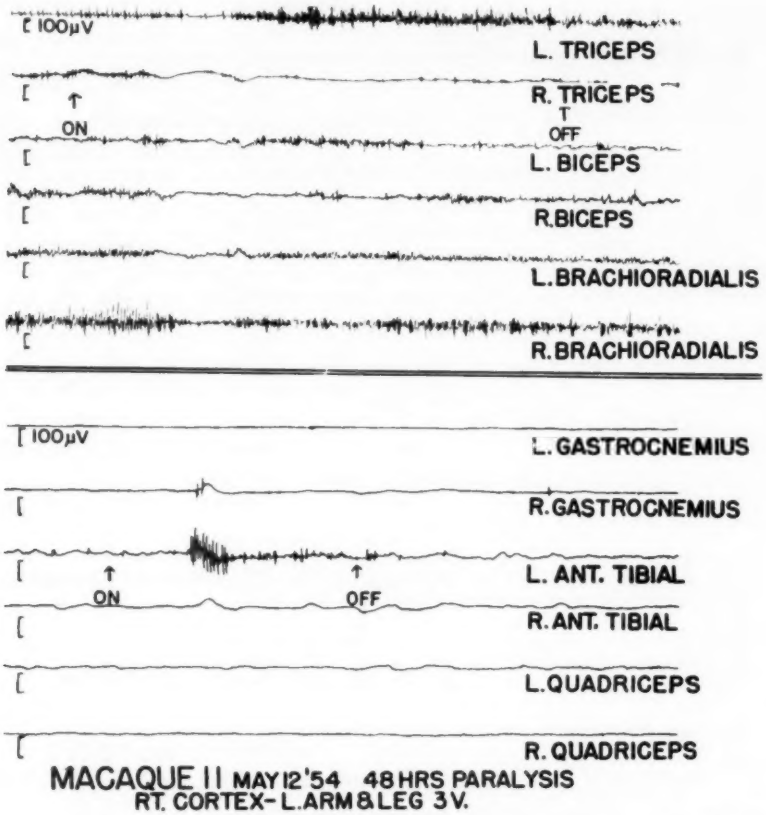


Fig. 3.—The experiment was commenced 48 hours after the onset of volitional weakness. Movements persisted only in the neck and tail, the limb girdle and extremity musculature being nearly flaccid. Deep reflexes were universally absent. There was significant respiratory embarrassment. The upper and lower tracings show the responses of extremity musculature to stimulation of the right motor cortex at 3 volts. Contralateral activation of the upper extremity musculature was confined to the left triceps, where there was considerable recruitment of new units during the stimulatory period. There was coincident lessening of tonic activity in the ipsilateral right triceps, and the ipsilateral brachioradialis showed transient activation at the beginning of stimulation. For the legs there was only transient activation of the left tibialis anterior, and this did not increase with stimuli at 15 volts.

of stimulation. The latter is interpreted as evidence that the cord internuncials were still functioning. Almost no tonic activity was recorded from the leg musculature at the sensitivity used in our usual experiment; and only the left tibialis anterior could be activated significantly at 3 volts. Raising the stimulus strength fourfold above this threshold did not increase the activation appreciably or spread the process to other muscles.

In the experiment illustrated in Figure 4 the results were similar. Again, the animal was quadriplegic when used, and the deep reflexes were absent. There was marked respiratory embarrassment without cyanosis. Histologically, we did not detect any completely normal motoneurones in either the cervical or the lumbosacral segments. In the cervical segments the cells showing Grade 1 damage exceeded those showing Grade 2 damage in the ratio of 2.5 : 1 on the left, and 4 : 1 on the right. For the lumbosacral cord cells showing Grade 1 and Grade 2 damage occurred in the ratio of 1 : 1 on the left and 1 : 1.5 on the right. Figure 4*A* shows activation of the contralateral right brachi-

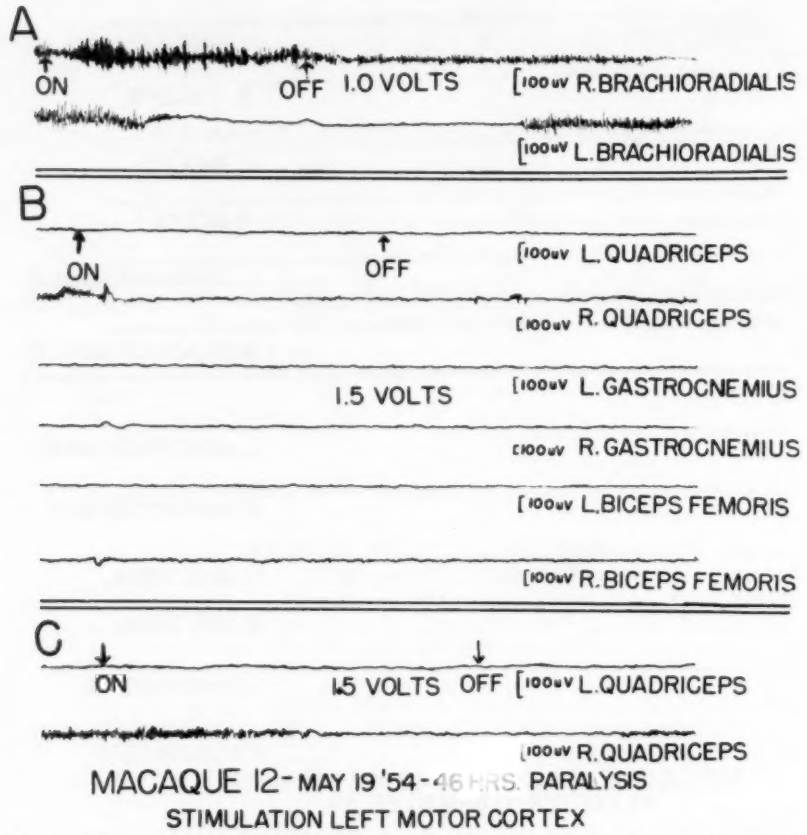


Fig. 4.—Paralysis developed gradually over a 46-hour period. When used, the animal was quadriplegic, retaining only the ability to adduct the left shoulder and to contract the right quadriceps muscle minimally. The upper pair of tracings (*A*, brachioradialis) illustate low-threshold activation of the contralateral right muscle with coincident but delayed lessening of tonic activity in the ipsilateral left one. Neither biceps nor triceps were activated significantly.

For the legs (*B*) only the right quadriceps could be activated at all from the left motor cortex leg area (threshold 1.5 volts). The response did not increase at 15 volts. In the lower two tracings (*C*) only minor recruitment of new units is evident against a background of tonic activity.

oradialis muscle with a 1-volt stimulus, with coincident reduction in amplitude of the tonic activity in the ipsilateral left muscle, which outlasted the stimulatory period significantly. In *B* (lower extremity) only the right quadriceps showed tonic activity, and that was lessened in amplitude by a 1.5-volt stimulus to the left motor cortex. Raising the stimulus strength threefold did not produce any further activation of the extremity. In *C* lessening of tonic activity followed minor activation of the same right quadriceps; tracings obtained coincidentally from the hamstrings showed no tonic activity and no activation. This experiment, too, demonstrates (1) the persistence of patterns of response indicative of internuncial action as long as there are functioning motoneurones to transmit the activity to the muscles, and (2) low threshold for cortical activation. We believe that the latter is to be attributed to the more normal of the remaining motoneurones, since significant increase in stimulus strength did not occasion a stronger response.

The subject of the final EMG experiment selected for illustration was a small animal which had received a relatively massive dose

of virus, thereafter passing through quite brief latent and preparalytic periods, to become profoundly paralyzed in all extremities four days after the injection. When the animal was used at 12 hours of paralysis, the musculature was atonic; tendon jerks were absent, and there was no volitional activity below the neck. Respiration was markedly impaired, and the lips appeared cyanotic. The only anesthesia possible was obtained through procaine infiltration of the scalp and tracheotomy incisions. Artificial respiration was maintained throughout. No tonic activity was evident in the EMG tracings from arm or leg musculature of either side, and stimuli below 40 volts did not produce any activation of the musculature of the extremities. However, 40-volt stimuli to the right motor cortex did produce slowly spreading seizures of the face and neck. As an accompaniment of these, visible clonic contractions appeared in the left coracobrachialis muscle. The poststimulatory discharge in that muscle is illustrated in Figure 5, by comparison with coincident silent tracings from the neighboring teres major and the gastrocnemius. Histological preparations from the cord were incomplete, but in the cervical segments examined many cells were in neuronophagia, in spite of the brief duration of the paralysis. It is believed that hypoxia contributed to the nearly complete unresponsiveness of this animal to cortical stimulation. The experiment also suggests that motoneurones no longer capable of transmitting ordinary activity may still have sufficient residual function to convey highly synchonized convulsive discharges.

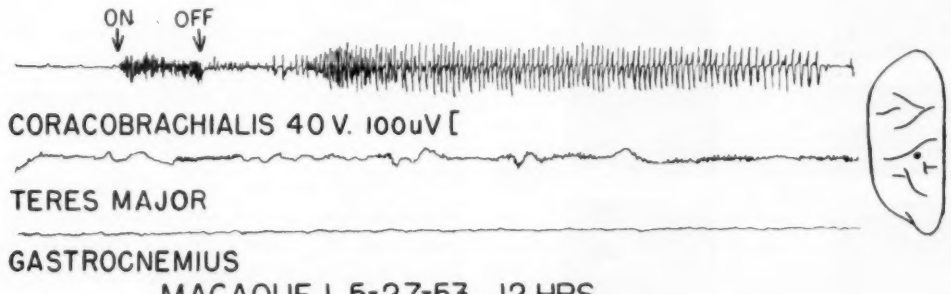


Fig. 5.—The preparalytic period was brief and the paralytic course fulminating; the animal showed complete flaccid paraplegia 12 hours after the onset of paralysis. There was so much respiratory distress (and cyanosis) that only local procainization of the incisions could be used for anesthesia. Respiration was maintained artificially throughout the recording.

Changes in the Two-Neurone Arc Discharge That Relate to the Development of Paralysis

The proprioceptor spinal arc, described in Lloyd's [2] classic study, was used to test the excitability of motoneurones damaged by virus. This two-neurone discharge is effected by direct transmission from the collaterals of dorsal root axons to the motoneurone somata. Campbell's [5] subsequent study of the effect of retrograde degeneration indicates that the two-neurone component is affected earlier and more significantly than is the multineurone one. Our study proves that a significant reduction in the two-neurone component coincides with the approach to maximal paralysis. The high amplification necessary to examine the multineurone component during the later stages of developing paralysis made it difficult to decide whether the longer latency elevations we recorded represented multineurone discharge or were occasioned through increase in synapse time and desynchronization incident to cell damage. Hence that phase of our study will require further investigation.

Figure 6 illustrates a series of tracings from experiments started at different times after the onset of paralysis. In each instance

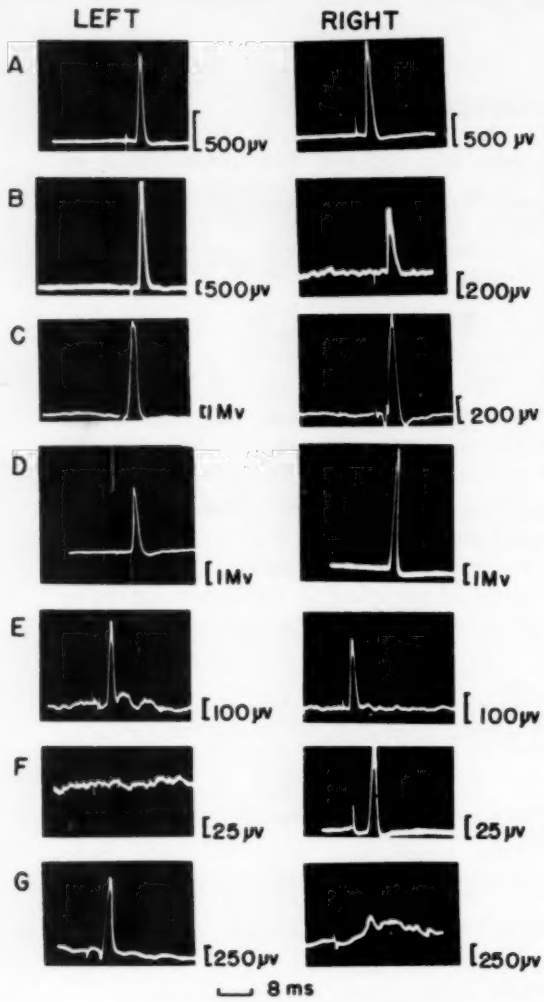


Fig. 6.—Records of the two-neurone reflex spike obtained from the L 7 ventral root subsequent to a brief electric shock given the corresponding dorsal root. *A*, normal preparation. *B*, the right sciatic nerve of a normal animal which had been crushed 30 days earlier to produce retrograde cell change in the corresponding motoneurones (see Fig. 7, right). Note that the right-sided response has significantly lower amplitude. *C*, four hours' paralysis (for this and the remaining pairs see Figures 7 and 8, respectively, for appraisal of histological damage and for plots indicative of the severity of cell involvement). *D*, 12 hours' paralysis. The disparity in amplification necessary to produce the tracings *E-G* as compared with *A-D* should be noted. Left-right differences in amplitude as between *C*, *D*, *F*, and *G* left and right are not always reconcilable with histological estimates of comparative cell damage upon the two sides.

the two-neurone reflex discharge over the L 7 ventral root was occasioned by a brief shock given the corresponding L 7 dorsal root. Figure 6*A*, left and right, are tracings from a normal animal introduced for comparative purposes. *A* and *B* left indicate the range of variation in amplitude observed in normal control preparations of our series. Reference to the calibration signals is necessary to evaluate the amplitude of the potentials further. *B* right, as compared with *B* left, shows the significant reduction in the two-neurone component which occurs as a result of retrograde cell change (Campbell [8]). *C* to *G* are representative potentials recorded under nearly identical conditions from the L 7 roots of Monkeys 4, 12, 16, 24, and 34 hours after the onset of paralysis.

The tracings of *C* were obtained from an animal in which volitional weakness of the right arm had appeared four hours previously. The left arm and both legs were used normally for climbing and jumping at the time the experiment was started. Preexperiment manipulation showed 2+ weakness in all movements of the right arm; the other extremities were normal, deep reflexes being neither exaggerated nor depressed. By comparison with the tracings from normal animals, the amplitude of the potential from the left root was quite large, that from the right reduced, findings to which we cannot attribute significance until more evidence has accumulated. However, such an amplitude difference between the left and the right potentials is in line with inequalities that we have observed in other experiments done in the late preparalytic period or in early paralysis. Histologically, the L 7 segment corresponding to Figure 6*C* showed motoneurones about equally divided between normal appearance and Grade 1 damage. No severely damaged cells were noted, and the number of mildly altered ones was about equal on the two sides.

In Figure 6*D* (12 hours) there was a marked disparity in amplitude between the left and right potentials; that recorded from the left root fell within the range of normal variation; that from the right seemed exaggerated. Examination prior to the experiment showed 2+ weakness in all movements of the arms and 1+ weakness in the legs.

The left ankle jerk and both knee jerks were absent, the right ankle jerk being 1+. Histological comparison with the four-hour specimen showed the number of normal-appearing motoneurones to be significantly increased. We did not observe a difference in the distribution of damage upon the two sides in spite of the disparity in amplitude of the potentials recorded.

For the 16-hour specimen, illustrated in Figure 6*E*, there was a marked reduction in potential amplitude by comparison with the preceding (note calibration signals). There was 3+ weakness in both lower extremities, and all deep reflexes were absent. Motoneurone damage in the L 7 segment was marked. No normal cells remained, and the number showing Grade 2 change was large. The amount of damage on the two sides was similar, and the interstitial inflammatory reaction was marked. Even so, there was still no difficulty in recording a potential from either ventral root.

The tracings from the 24-hour specimen, illustrated in Figure 6*F*, show an even more marked loss in potential amplitude. No two-neurone or multineurone component was recorded on the left at any stimulus strength, and the potential of the right side was notably reduced by comparison with the 16-hour specimen. The remainder of normal-appearing motoneurones was small. Weakness in both legs was 3+, but had been evident longer on the right. The right ankle jerk was 1+; that of the left, absent. The left knee jerk was reduced; that of the right, somewhat overactive.

In the 34-hour experiment (Fig. 6*G*) the two-neurone potentials had a somewhat higher amplitude than in the preceding one. A left-right difference also existed, the left potential being the larger. Except that Grade-2-damaged motoneurons exceeded in number those showing Grade 1 change, the damage was approximately like that seen in sections of the 24-hour animal and was nearly equal upon the two sides. However, there was a significant disparity in weakness of the legs, 2+ for the left and 4+ for the right (complete flaccidity). All lower extremity deep reflexes were absent.

The reduction in the two-neurone potential during the approach to maximal parlysis should correlate better with the histological than with the clinical appraisal of damage, since electrophysiological and histological data relate to the same cord segment, whereas tests of weakness are referable to intersegmental activity. We noted that in the early hours of paralysis there might be no reduction, although significant early motoneurone damage had already occurred. In some instances the two-neurone potential even appeared exaggerated in the early hours of paralysis, and we had difficulty in reconciling the size of the deflection from a root with the extent of the damage to the motoneurones. Thus, we concluded that potential amplitude in early paralysis might average two effects: (1) exaggeration due to brain stem disturbance effecting release of the more normal motoneurones, and (2) loss in excitability, due to reduced functioning of the more affected ones. Bodian [8] has called attention to spasticity in early experimental poliomyelitis, and also conjectures about the effect of brain stem lesions upon the motor activity of infected animals.

When a marked reduction in amplitude of the two-neurone potential has appeared (usually 12-16 hour paralysis) it has been associated histologically with a relative absence of normal-appearing motoneurones in the segment and with a significant increase in the number of those which show Grade 2 change. Then, left-right disparities in potential amplitude may bear a clear relationship to the clinical estimate of weakness, although this is not invariable. No completely normal motoneurones were observed in the 16-hour experiment, and we believe it important that we were able to record two-neurone potentials of reasonable size from both ventral L 7 roots, thus indicating conclusively that affected motoneurones must remain, for a time at least, accessible to synaptic activation.

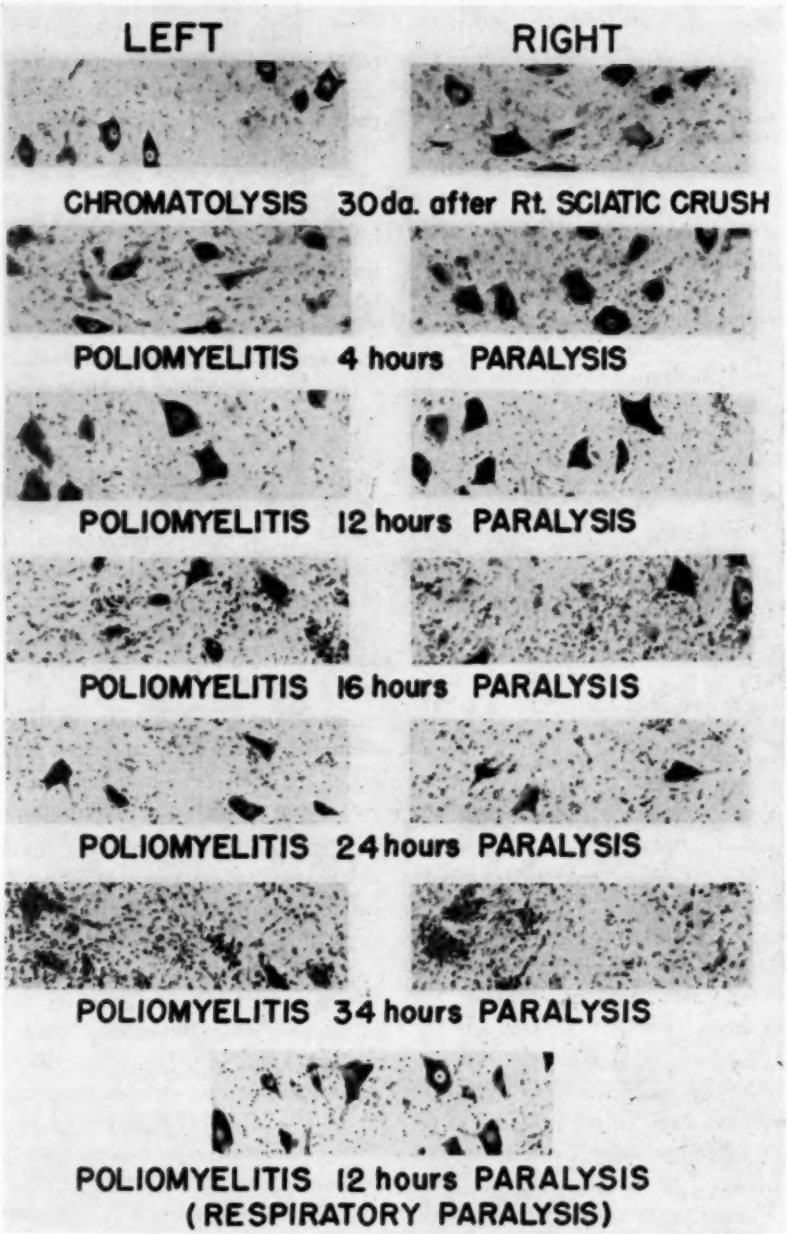


Fig. 7.—Photomicrographs of motoneurones of the L 7 segments from which records *C-G* of Figure 6 were obtained. Motoneurones corresponding to the tracings of Figure 12 are also included. Other references are given in the text. Areas selected for photography were considered typical of the involvement in the particular preparation.

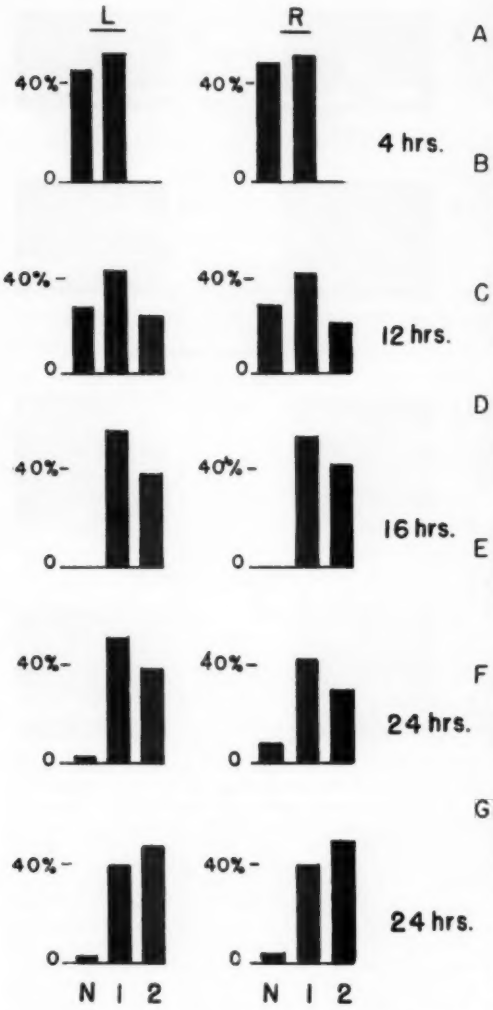


Fig. 8.—Proportions of motoneurones showing normal appearance and Grade 1 (mild) and Grade 2 (severe) cell change based on counts of the L 7 segments of infected animals illustrated in Figures 6 and 7.

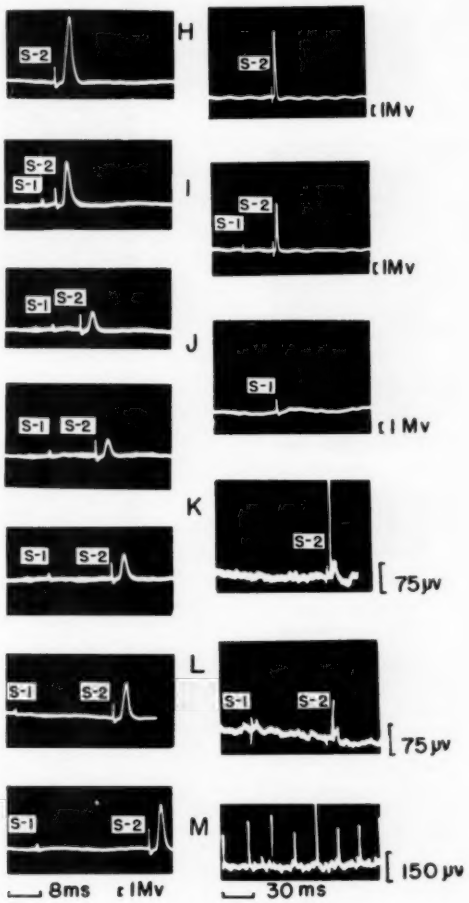


Fig. 9.—*A* to *G* represent a series of two-neurone reflex spikes (four hours' paralysis, Figs. 6, 7, and 8) recorded at intervals of three seconds. A weak electrical shock (Stimulus *1*) to the L 6 dorsal root, which was subliminal for an L 7 response, produced relative refractoriness of the L 7 motoneurones, as activated by a second stimulus (*2*) to the dorsal root. *A*, control record, showing the L 7 activated spike without a preceding dorsal L 6 stimulus. In *B*-*G* the L 6 dorsal root stimulus was introduced at increasingly longer intervals before the L 7 one. Note that the refractoriness is maximal at a separation of 8 to 12 msec. between stimuli. *H*, *I*, and *J* are upon a slower time line, with a longer interval separating the successive stimuli. *H*, control; *I*, the L 6 shock precedes the L 7 one by 30 msec.; *J*, stimulation of L 6 alone did not result in an L 7 activated spike. *K*, *L*, and *M* are from the animal paralyzed for 16 hours. Comparison of *K* (control) with *L* (preceded by the L 6 shock) shows a similar finding on a slow time line, the first shock preceding the second by 65 msec. Under the circumstances of experiment the relative refractoriness of the L 7 motoneurones persisted at least 65 msec. subsequent to the first stimulus. *M* shows that the motoneurones follow repetitive stimuli at 30-msec. intervals.

Other Properties Examined in the Two-Neurone Preparation

Elaboration of the technique described in the preceding section permits examining other properties of motoneurones. Renshaw,[6] Lloyd,[7] Pitts,[8] Clare, Mills, and Bishop,[9] and Grundfest and Magnes[10] have studied various aspects of facilitation and of relative refractoriness in the reflex path. Their studies in normal animals have guided our endeavor.

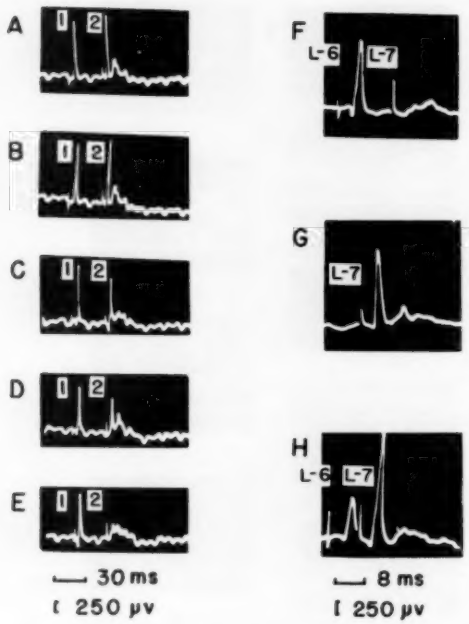


Fig. 10.—*A-E*, 34 hours' paralysis; left dorsal to ventral L 7 response; slow time line. The successive pairs of responses resulted from shocks of the same strength given at 30-msec. intervals, each pair being separated from the next by approximately 3 sec. Note progressive reduction in size of the second of the paired responses, until in *E* it fails almost completely. *F-H*, faster time line in the same experiment. In *F* the L 6 dorsal root shock had sufficient intensity to produce a submaximal L 7 reflex spike. When followed at a 14-msec. interval by an L 7 dorsal root shock, the reflex spike resulting from the latter was largely occluded. In *H*, the strength of the L 6 activating shock was reduced to diminish the size of its L 7 reflex response, and the two shocks were brought closer together. The result was facilitation of the L 7 reflex potential. Reference to Figure 8 will show that few motoneurones of this preparation could still be considered normal.

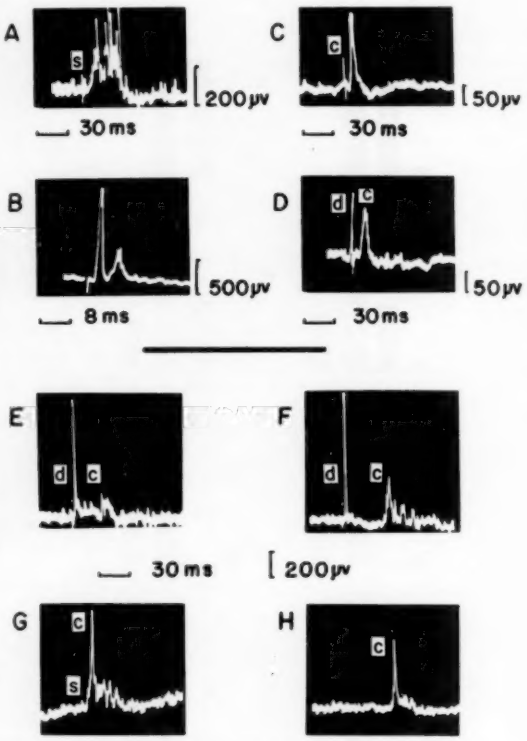


Fig. 11.—L 7 root potentials evoked from stimulation of contralateral cortex and ipsilateral reticular substance; animal paralyzed for 16 hours. No completely normal motoneurones remained in the L 7 segment. Other tracings are illustrated in Figures 6 and 9. *A*, left ventral L 7 potential evoked by single-shock stimulation (*s*) of the right motor cortex leg area; slow time line. Clusters of spikes characterize the record presented. In other records the spike clusters had briefer duration. *B*, potential evoked from the same root subsequent to stimulation of the left mesial medullary reticular substance at a level 2 mm. rostral to the obex. *C* and *D* are tracings from the right ventral L 7 root. In *C* L 7 potential was evoked from a single shock applied to the right mesial reticular substance (*c*) at a level comparable to that of *B*. In *D* the reticular-evoked potential (*c*) was recorded from the left L 7 ventral root subsequent to a dorsal-root-activated volley (*d*). The dorsal-root-activated volley (*d*) in records *E* and *F* was succeeded by a cortically activated volley (*c*), which is notably reduced by comparison with *G* and *H*, in which the first shock and its corresponding volley were omitted.

For this purpose a subliminal dorsal L 6 stimulus was made to precede and condition the response of ventral L 7 to a dorsal L 7 stimulus. It is perhaps significant that, through manipulation of the relative strengths of the two stimuli, we were able to show facilitatory effects at a stimulus separation of several milliseconds, even in the animal that had been paralyzed for 34 hours (Fig. 10, compare *H* with *G*). In that animal a marked reduction in amplitude of the two-neurone potential had already developed; and, as illustrated in Figure 10 *A-E*, the L 7 volley itself showed definite fatigue when successive pairs of shocks of the same stimulus strength were applied to the dorsal L 7 root. With 30-msec. separation between the members of each pair and 3-sec. intervals between pairs, the volleys resulting from the second shocks were successively reduced. Since few remaining nor-

mal motoneurones were available for facilitation, the result suggests that the process must have occurred in already altered ones.

Figure 9, *A-G*, from the animal in which paralysis had commenced four hours earlier, illustrates a cycle of relative refractoriness initiated by a subliminal L 6 conditioning shock and manifest from reduction in the amplitude of the ventral L 7 volley activated by the succeeding dorsal L 7 stimulus. The conditioning stimulus is labeled *S-1* in this instance, and the test stimulus *S-2*. It is to be noted that the motoneurones were least responsive to the test stimulus when the latter followed the conditioning one by an interval of 8-12 msec. Comparison of *H*, *I*, and *J* indicates the degrees of refractoriness that persisted with 30-msec. separation between shocks, and of *K* and *L* for 65-msec. separation in the animal paralyzed for 16 hours, referred to previously. In that animal the L 7 ventral root volley followed repetitive dorsal root stimuli at 30-msec. intervals, even though some variation in amplitude was apparent (Fig. 9*M*).

Relative Refractoriness of Cortical- and Reticular-Activated L 7 Volleys When Preceded by the Two-Neurone Volley

In each of this series of experiments the effort was made to record the ventral L 7 volleys resulting from activation of the contralateral leg area of the motor cortex, and of the ipsilateral reticular formation. If internuncials continue to operate as long as the motoneurone pools function, the losses should be parallel. In the case of cortical stimulation only single shocks were used, and no effort was made to follow the course of facilitation which Bernhard and Bohm [11] found to occasion the appearance of a *CM* (single synapse) component of the path from cortex to muscle in the monkey. In interpreting the results of reticular stimulation, we have followed Lloyd's [2] study of the bulbospinal correlation system.

Traces from the monkey paralyzed for 16 hours are used for illustration (Fig. 11) because of the universal damage to L 7 motoneurones evident there. Trials in this, and in other animals, show additionally, we believe, that damaged motoneurones are activatable from these sources for as long after the onset of paralysis as we previously indicated for root-activated potentials, permitting the inference that the internuncials are at least as resistant to damage as are the motoneurones.

For the 16-hour animal an L 7 root potential, consisting of a cluster of spikes, was recorded as the response to contralateral leg area stimulation by a single shock. It is illustrated in Figure 11*A*. Somewhat later in the experiment, better synchronized cortically evoked L 7 volleys were recorded (*G* and *H*). *B* and *C* of Figure 11 are typical of L 7 volleys activated from the ipsilateral mesial reticular substance.

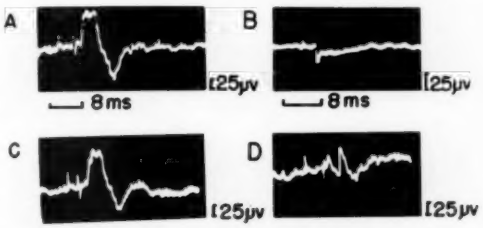


Fig. 12.—When used at 12 hours' paralysis the animal showed complete quadriplegia and Biot's breathing. While it was being prepared, Cheyne-Stokes respiration set in. Tracings *A* and *C* show almost identical low-amplitude, slow L 7 ventral root potentials evoked by brief electric shocks applied to the left L 7 dorsal and lateral columns, respectively. Upon the right side (*B* and *D*) no activation resulted from the L 7 dorsal root stimulus, and but a trace potential from stimulation of the left lateral column. Typical cells illustrated at the bottom of Figure 7 were quite dark but did not give the appearance of advanced change characteristic of severely virus-damaged preparations, from which much better ventral root potentials were recorded. The marked loss of responsiveness is presumed to result from hypoxia superposed upon virus damage.

The dorsal-root-activated two-neurone potential can render the motoneurones relatively refractory to cortical or reticular stimulation. The time course corresponds with that shown for L 6-L 7 dorsal root stimuli. In *D* of Figure 11 a dorsal-root-activated potential (*d*) preceded the reticular-activated one (*c*) by 16 msec., lessening

the amplitude of response to the latter (compare with *C*). Other dorsal-root-activated reflex potentials, illustrated in *E* and *F*, preceded volleys in the same ventral root activated from the contralateral cortex. With intervals of 30 and 40 msec., respectively, between conditioning and test shocks, the amplitudes of the cortically evoked volleys (*c*) were significantly reduced by comparison with *G* and *H*, in which the conditioning shocks were omitted.

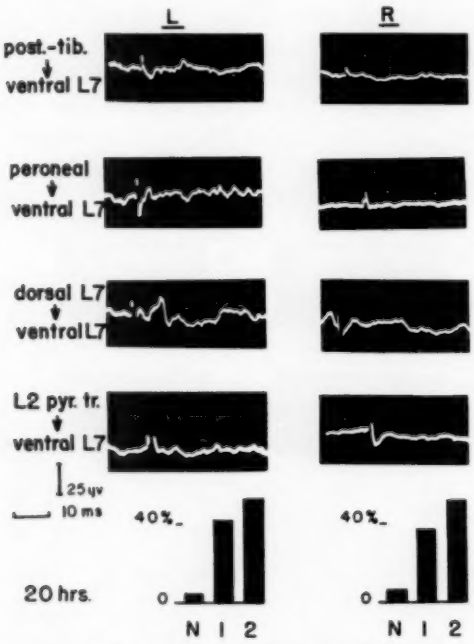


Fig. 13.—In this animal, quadriplegic at 20 hours' paralysis, the respiratory embarassment was identical with that for the experiment illustrated in Figure 11. Note that no significant potentials were recorded either from L 7 ventral root from stimulation of corresponding posterior tibial and peroneal nerves, or from the L 7 dorsal root or lateral column. In this instance there was much Grade 2 (severe) cell change, but numerous cells showed only Grade 1 alteration.

Some Effects of Hypoxia

Certain of our EMG studies indicated that cumulative hypoxia could further reduce the excitability of virus-damaged motoneurones. Several experiments of the lumbosacral cord series also support this view. In Figure 12 tracings are presented from an animal that was found to be completely quadriplegic and showing Biot's breathing 12 hours after the onset of paralysis. Deep reflexes were absent. We were able to initiate only minor L 7 ventral root potentials from stimulation of either the corresponding left dorsal root or the upper lumbar lateral fiber column. These were nearly identical. Histologically the motoneurone damage was surprisingly light (Fig. 7, bottom), considering the severe quadriplegia. Cells showing Grade 2 damage were not evident in the L 7 segment.

Another animal showing flaccid quadriplegia and marked respiratory impairment was used at 20 hours. Histologically, the extent of cell damage was usual for this stage (Fig. 13). Even with strong stimuli it was impossible to evoke ventral L 7 potentials from stimulation of ipsilateral tibial or peroneal nerves, the dorsal L 7 root, or the upper lumbar lateral column. At a corresponding stage we were successful in doing so in animals that did not show significant respiratory involvement. Thus, this evidence, too, supports the role of hypoxia as a factor contributing to the marked reduction in motoneurone excitability indicated.

Comment

Too little is known of the electrophysiological alterations during acute poliomyelitis, or related virus affections of the nervous system in general. The experiments we report herein have value in defining areas worthy of meticulous investigation. Such studies are feasible, for, without unusual effort, we have been able to maintain paralyzed animals in good condition during recording that has lasted four hours or more. Few animals have been lost through experimental failure, indicating that more critical investigations (such as microelectrode recording from virus-damaged motoneurones) can be undertaken with a fair chance of success.

Our findings reemphasize the motoneurone as the chief target of this virus. In experiments utilizing motor cortex stimulation and EMG recording, we found that during

the approach to maximal paralysis distal movements could often be evoked by repetitive cortical stimuli having a threshold little in excess of that found for normal animals. EMG activation of more proximal muscles also occurred with stimuli near the same strength. Considering the number of severely altered motoneurones and the interstitial inflammatory reaction evident in the cords of some such animals, the low thresholds found are somewhat surprising. However, we believe that the remaining, nearly normal cells provide this residual low-threshold path, for increasing the stimulus strength often did not evoke a brisker or more powerful contraction. If the muscles showed little tonic activity, they were usually activated minimally at any strength of stimulation. Finally, with complete flaccid paralysis of an extremity, only powerful repetitive stimulation, such as readily occasions convulsion in normally innervated muscles, may bring about a sufficiency of central synchronization to force the synaptic barrier of the depressed motoneurones. Activation of the muscles thus occasioned is likely to continue as poststimulatory after-discharge. Thus, even though the virus strain used here is likely to occasion rapid necrotization, the depressed motoneurones may pass through a stage in which they are still excitable to extraordinary stimulation.

Correlations of the clinical severity of acutely developing paralysis, the reduction in amplitude of the two-neurone potential, and the histological estimate of the extent and severity of motoneurone damage require special consideration of the early hours after the onset of paralysis. Then the two-neurone potential may still approximate the normal in amplitude, or perhaps be exaggerated, even though many motoneurones show Grade 1 damage. When exaggeration has occurred, we have attributed it to a release phenomenon occasioned by brain stem lesions. As neuronophagia becomes increasingly prevalent and the interstitial reaction more marked, we have found that the amplitude of the two-neurone potential becomes significantly reduced. In the instances where disparities in size have occurred between the two-neurone potentials of the two sides, the greatest decrease has usually occurred on the side of the more marked clinical weakness. Such disparities in amplitude have less often reflected corresponding disparity in the motoneurone damage to left and right hemisegments of the cord.

Our experiments upon the lumbosacral cord also permit comparison of the loss of activation of the proprioceptor (two-neurone) potential and of the same motoneurones through the long tracts that arise in the contralateral cortex and ipsilateral reticular formation. In the instance of corticospinal activation by single shocks it seems likely from the prior studies of Lloyd [13] that internuncial cord mechanisms must relay the impulses from long-tract terminals to motoneurones. The sequence of loss in the two instances is roughly parallel. Exceptions have occurred, but not noteworthy ones, and from the finding we infer that the internuncial mechanisms operate at least as long as the motoneurones are able to transmit activity to the muscles. EMG experiments provide other evidence that internuncials continue to operate in the acute phase of paralysis. For example, the lessening in tonic activity in one muscle occurring coincidentally with activation in another suggests that internuncial pools still pattern the outflow. However, to test the "internuncial lesion" theory of muscle spasm in poliomyelitis will require further studies by direct internuncial recording.

The studies upon facilitation and relative refractoriness of virus-damaged motoneurones in monkeys are not sufficiently complete to warrant comparison with normal data which are available for cats. However, they indicate the feasibility of using such comparisons as an index of disturbance in the relatively long-enduring processes of the reflex path. Thus amplification of the data may shed further light upon that physi-

ological dissolution of the nerve cell which is occasioned through virus action.

Our observations bear only an indirect relation to recent emphasis upon lesions in the reticular substance of the brain stem in cases of fatal human poliomyelitis. One aspect concerns the possibility that in the early hours of paralysis lesions there may effect a release of certain motoneurones from the inhibitory action of medullary centers. Another relates to the unresponsiveness of the neural mechanisms of the lumbosacral cord in monkeys which showed respiratory embarrassment before recording was commenced. The findings in certain of our experiments suggest that cumulative hypoxia resulting from central respiratory impairment can add significantly to the motoneurone damage occasioned by the virus. In a recent histological study of seven cases of fatal human poliomyelitis, Barnhart, Rhines, McCarter, and Magoun [4] state that the severe brain stem lesions were distributed in the central core, with characteristic injury to the reticular formation and tegmentum. In those of our experimental animals in which the brain stem sections were examined in detail, we encountered disseminated inflammatory lesions more frequently. In trials to activate the motoneurones over the proprioceptor paths of such animals, the reticular activation persisted as long as did the two-neurone proprioceptor potential. Without minimizing the role reticular lesions may play in contributing to the severity of the manifestations, for monkeys displaying chiefly spinal paralysis the role of motoneurone damage would appear to be the primary one.

Kaada [15] did EMG studies upon monkeys in the preparalytic and acute paralytic stages of experimental poliomyelitis. He emphasized the low threshold of the muscles to stretch and the ability of single motor units to discharge continuously at a low frequency (5-20/sec) for a long period in response to maintained slight stretch. He also believed that the action potential in the paralytic period can be recorded simultaneously in antagonistic muscles during voluntary contraction. Denny-Brown and Foley [16] also studied the course of the disease in monkeys by electromyographic methods, finding that abnormality in the discharge rhythms was the first sign of the disease, preceding fever and paralysis by several days. This change was associated with an increase in all reflex discharge from the centers, including the stretch reflex. Immediately preceding paralysis the affected units discharged in bursts of high frequency, and the last discharges recorded before necrosis of motoneurones were brief bursts of 3 to 50 beats at 240-350/sec. Evidently their recording was done in unanesthetized preparations and with equipment that exceeded our electroencephalograph in resolving power. The method of activation also differed. Thus, we are reluctant to draw comparisons with our work.

SUMMARY

Eight normal monkeys and 22 infected with the Lansing strain of poliomyelitis virus (intracerebral inoculations) were used for (1) motor cortex stimulation and electromyographic recording, and (2) L 7 ventral-root recording of the two-neurone (proprioceptor) volley and those responses resulting from single-shock stimulation of contralateral motor cortex and ipsilateral reticular substance. The experiments were controlled histologically.

The experiments yielded additional information concerning the loss of motoneurone excitability that occurs as a result of virus damage. Persistence of low threshold to cortical activation as paralysis develops, together with lessening in, and then loss of, the increment of briskness and strength of contraction as the stimulus is increased, suggests that the least damaged of the motoneurones provide the residual low-threshold path. As complete flaccid paralysis develops in an extremity, particularly when the effects of virus damage are complicated by presumptive hypoxia due to respiratory impairment, the remaining motoneurones may become nearly, or wholly, unresponsive.

During the approach to maximal paralysis, cortically initiated lessening of tonic activity in one muscle can coincide with activation in another, suggesting that the internuncials still operate in determining the pattern of outflow.

At the beginning of paralysis, even when mildly damaged motoneurones are frequent, the amplitude of the two-neurone potential may not be markedly reduced, and in some instances may even appear exaggerated. Later the two-neurone potential becomes much reduced in amplitude, the degree of reduction relating generally to the reduction in number of normal motoneurones and to significant increase in those showing severe damage. The disappearance of the two-neurone potential also parallels the growing inaccessibility of the same motoneurones to activation from contralateral cortex or ipsilateral reticular substance.

Drs. Sidney Goldring, Herbert Rosenbaum, and William Collins aided in certain phases of the study. Dr. Robert Denton, Malcolm McGavern, and Richard Dewey did the cell counts.

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Mechanisms of Skeletal Muscle Pain and Fatigue

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Lewis [1] postulated that pain in ischemic, active muscles was brought about by the accumulation in the tissue spaces of a metabolite which he designated as "Factor P." He also indicated that Factor P was the stimulus responsible for the pain of intermittent claudication and coronary occlusion. In these syndromes the pathologic process leading to obstruction of vessels supplying blood to the active muscles was the key to the production of pain. Recent investigations of headache and backache syndromes * demonstrate that sustained skeletal muscle tension can evoke pain in the absence of pathologic involvement of either the blood vessels or the muscles. In light of evidence † indicating that tetanic contractions cause reduction in muscle blood flow, it seemed desirable to explore the hypothesis that the pain mechanisms in these syndromes were essentially those involved in the genesis of ischemic muscle pain. The following experiments concerning the relationship of skeletal muscle activity, muscle blood flow, and muscle pain in human subjects were, therefore, undertaken.

METHOD

Ten young, healthy adults, 8 men and 2 women, were subjects for the experiments. Skeletal muscle contractions were performed by squeezing with the fingers a rubber bulb attached by rubber tubing to a mercury manometer graduated in centimeters. The thumb was not used in the contraction. The level to which the mercury was raised by the contraction was termed the "contraction strength." A strong contraction strength of 11 cm. Hg was employed most commonly. The term "endurance contraction" refers to contractions held by the subject for the maximum amount of time possible. During the experiments the subjects were in a reclining position, with the forearm in a comfortable extended position at heart level. Circulation to the exercising forearm in some experiments was arrested by inflation of a sphygmomanometer to pressures exceeding 200 mm. Hg. Muscle pain intensity was measured on a 1 to 10 scale, 10 being comparable to the maximum degree of pain in the subject's experience. Pain threshold as used here refers to the time required for pain to appear in a given contraction.

Muscle temperature was measured by copper-constantin thermocouple wires inserted in a 23-gauge needle and placed to a constant depth of 20 mm. in the forearm flexor muscles. A plastic guard attached to the head of the needle and secured to the arm with cellophane tape prevented deeper penetration. Muscle temperature determinations were read directly from a potentiometer or amplified and recorded on a Leeds & Northrup Model S Speedomax Type G Potentiometer Recorder. The potentiometer was a Leeds & Northrup Double Range Portable Precision instrument with a built-in lamp and scale galvanometer, with a range of 0 to 80.5 mv. A Leeds & Northrup Stabilized D. C. microvolt-indicating amplifier was used with the Speedomax Recorder. The reference junction was kept in a 0 C ice bath. Experiments were conducted under uniform conditions at a room temperature of 26.0 C.

EFFECT OF SUSTAINED AND RHYTHMIC SKELETAL MUSCLE CONTRACTIONS ON SKELETAL MUSCLE BLOOD FLOW: EVIDENCE FOR ISCHEMIA CONTRIBUTING TO GENESIS OF PAIN IN CONTRACTING SKELETAL MUSCLE

Experiments were devised to compare the characteristics of pain produced in muscle contractions with circulation arrested and

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* References 2 to 4.

† References 5 to 9.

with circulation intact. Both rhythmic and sustained contractions were studied.

Comparison of Pain Characteristics in Sustained Contractions with Circulation Intact and with Circulation Occluded

With circulation occluded, strong, gripping contractions of the hand, at the rate of one per second, were performed by three subjects. After suitable rest periods the experiments were repeated with the circulation intact. Pain was produced in each instance and the characteristics were similar both qualitatively and quantitatively. The pain threshold was shorter when the circulation was occluded (45 to 60 seconds) than when the circulation was intact (70 to 90 seconds).

Figure 1 is a record of pain production during two 11-cm. sustained contractions: one with circulation arrested and the other with circulation intact. Six other exercises of the same type gave almost identical results. The contraction with circulation arrested was held for a maximum length of 150 seconds, at which time the amplitude of the contraction involuntarily fell. The pain did not stop with cessation of the exercise but persisted until the circulation was restored, at which point it subsided within a few seconds.

During the initial 150 seconds of the experiment with intact blood flow, the endurance and production of pain were similar to the above observations. However, with the involuntary fall in contraction amplitude, the ability to maintain the contraction was partially restored, and the exercise could be continued for 10 minutes with only low-intensity pain. The pain disappeared promptly when the contraction was released. During similar experiments, in which the contractions were terminated at the limit of endurance, the pain promptly subsided coincident with relaxation of the grip.

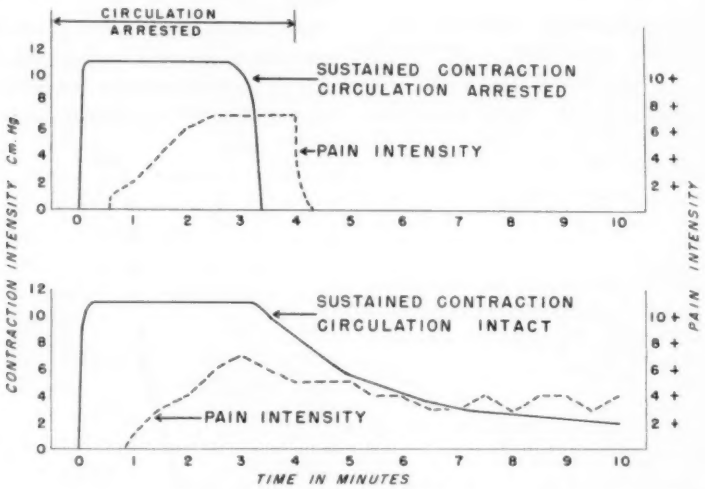

Fig. 1.—Comparison of 11-cm. contractions with circulation intact and with circulation arrested.

The pain produced during the contractions in the above observations was deep, dull, and poorly localizable and was experienced in the area of the active muscles. Preceding the onset of pain, sensations of discomfort in the muscles were often noted. Deep tenderness in the contracting muscles could frequently be elicited just prior to the onset of pain and immediately following the disappearance of pain.

Comment. — These observations indicate that strong rhythmic and sustained skeletal muscle contractions performed with blood flow intact are productive of pain with qualitative and quantitative characteristics indis-

TABLE 1.—*Comparison of Sustained Contractions at Different Contraction Strengths with Circulation Intact and with Circulation Arrested*

	Maximum (16 Cm. Hg)		Strong (11 Cm. Hg)		Weak (5.5 Cm. Hg)	
	Circulation Arrested	Circulation Intact	Circulation Arrested	Circulation Intact	Circulation Arrested	Circulation Intact
Pain threshold, sec.	25	35	32	55	63	330
Endurance, sec.	80	92	130	155	320	More than 25 min.
Pain intensity	7+	7+	7+	7+	6+	3+

tinguishable from ischemic muscle pain. The similarity in endurance, pain intensity, and pain threshold observed with intact blood flow and with occlusion suggests that a state of relative ischemia is a common denominator in the two types of contractions.

Relation of Contraction Strength to Pain Threshold

In Figure 1 it was noted that in the sustained contraction with the blood supply intact, a diminution of the contraction strength was associated with renewed and prolonged muscle endurance and a decrease in pain intensity. One possible explanation is that the involuntary decrease in contraction strength was associated with a relative increase in blood flow.

The similarity between contractions under conditions of intact and occluded blood flow was found to be most marked in maximal contractions (Table 1, Fig. 2) and least evi-

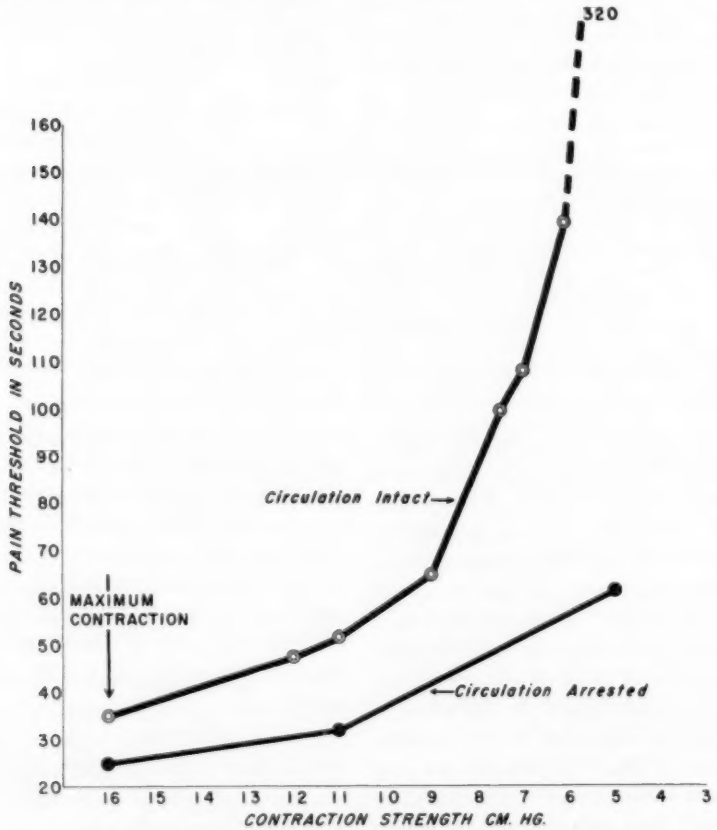

Fig. 2.—Relation of contraction strength to pain threshold.

dent during weak contractions. In the weak, 5.5-cm., contraction pain with circulation intact was of low intensity in comparison with similar contractions done with circulation occluded.

Figure 2 shows the almost straight-line relationship which exists between the strength of a sustained contraction performed with circulation arrested and the pain threshold. A different curve is evident when the pain threshold is plotted against the contraction strength when the blood flow is intact. Values plotted are the averages of two determinations on one subject and are representative of the subjects studied.

Comment. — It may be inferred from the pain-threshold and contraction-strength curves that the rate of the pain process, i. e., the rate of Factor P production, is proportional to the contraction strength, or rate of metabolism in the muscle. Under conditions of intact blood flow, weakly contracted muscle receives more blood than strongly contracted muscle. Consequently, more of the noxious, pain-producing factor is either dispersed or inactivated during a weak contraction with intact blood flow than occurs during a strong contraction. Although it has been demonstrated that muscle blood flow during a weak contraction rises slightly above the base level,[8] it would appear that the increase is insufficient to meet the metabolic requirements of contracting muscle. The pain threshold, then, appears to be a function of contraction strength and muscle blood flow.

Skeletal Muscle Temperature Changes with Sustained Contractions

The similarity of the pain threshold, pain intensity, and endurance for the maximal contractions observed above (Table 1) suggests that during a sustained contraction with intact blood flow the degree of ischemia is similar in magnitude to that occurring during a sustained contraction with circulation occluded. This, again, suggests that muscle contraction itself mechanically interferes with blood flow into the muscle and that the degree of vascular obstruction is proportional to the contraction strength.

In an attempt to assess blood-flow changes in contracting skeletal muscles, a series of 29 experiments with six subjects was performed in which muscle temperature in the forearm flexor muscles was measured during sustained contractions. In 19 of these experiments continuous rectal temperature determinations were done. Contractions ranging from 1 cm. to maximum contraction strength were performed.

In experiments in which the contraction strength was approximately 50% or more of maximum, there was an initial, short-lived fall in muscle temperature (Fig. 3). The decrease in temperature was about 0.1 degree (C) and extended for as long as 35 seconds, although in most contractions the temperature returned to the base line within 30 seconds. No fall in temperature was seen at the onset of weak contractions or in any contractions performed with the blood flow occluded.

Muscle temperature rose after the initial depression in the strong sustained contractions (11 cm. Hg) with blood flow intact and immediately in the weaker contractions (5 cm. Hg). The muscle temperature rose rapidly and remained elevated for several minutes at the conclusion of strong contractions with intact blood flow and when the circulation was restored in contractions done with occluded blood flow.

During two exercises involving strong contractions, the muscle temperature for a short time rose above the rectal temperature. On these occasions cessation of the exercise brought with it a brief fall in temperature.

Comment.—With the two exceptions noted above, the muscle temperature was less than the rectal temperature. Hence, the blood entering the muscle may be assumed to be warmer than the muscles. Blood temperature in the brachial artery has been found under ordinary conditions to be within approximately 1 degree of rectal temperature.‡ The brief muscle temperature depression

‡ References 10 and 11.

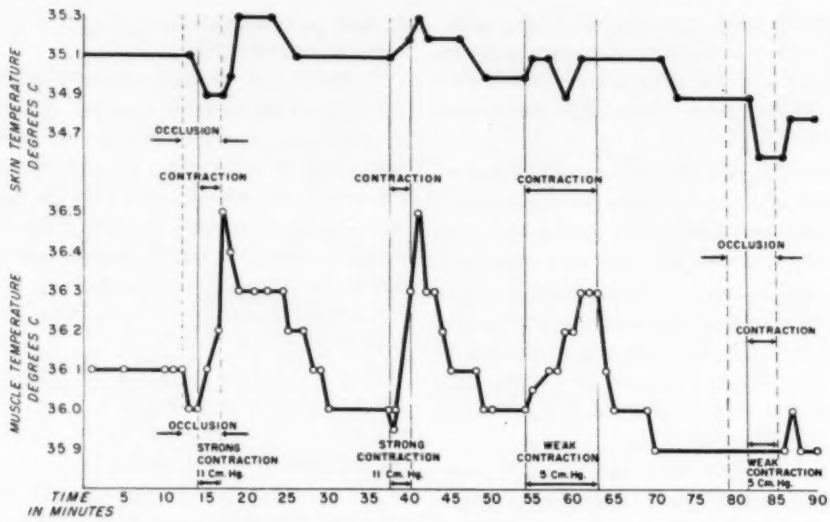

Fig. 3.—Skeletal muscle temperature changes during weak and during strong contractions with circulation intact and with circulation arrested.

occurring at the onset of strong contractions has been observed previously [12] and is considered to indicate a decrease in the blood flow. The temperature elevation following the exercise is attributed to the postcontraction hyperemia § mediated by release of local vasodilating substances.‖ Under conditions of both intact and occluded blood flow, the striking similarity between temperature curves of the strong contractions and the marked difference between the temperature curves of the weak contractions (Fig. 3) suggest, again, the relation between contraction strength and muscle blood flow.

§ References 8, 13, and 14.

‖ References 15 and 16.

Skeletal Muscle Temperature Changes with Rhythmic Exercise

Figure 4 records the muscle temperature changes occurring during rhythmic exercise. Two subjects performed eight experiments in which the forearm muscles were alter-

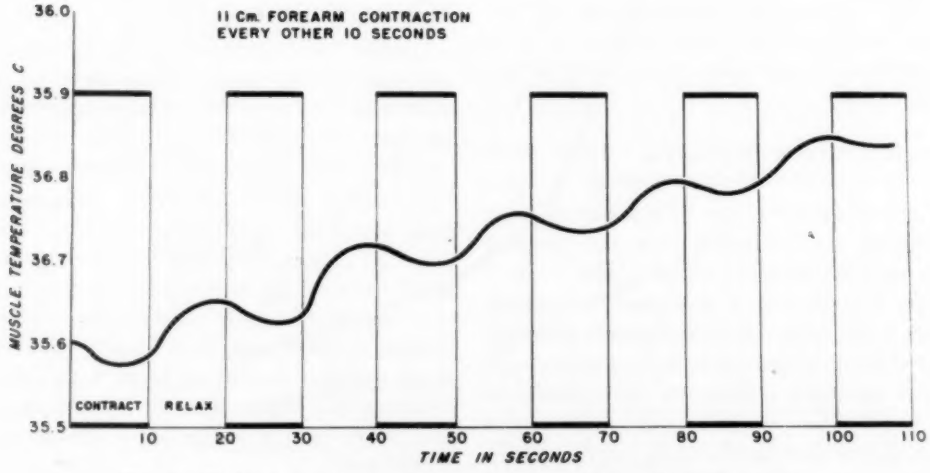

Fig. 4.—Skeletal muscle temperature changes during a rhythmic exercise.

nately contracted for 10 seconds and then allowed to rest 10 seconds. For approximately the first two minutes of the exercise, each contraction was associated with a fall in muscle temperature, with a rise in temperature during the relaxation period. The net change was a slow, stepladder-like rise in temperature. After two to three minutes, as muscle temperature approximated core temperature, the cyclic changes in muscle temperature became diminished in amplitude. been recorded. The values plotted are the averages of from two to eight experiments performed for each type of exercise.

The temperature of the water bath was held constant during each experiment but varied from experiment to experiment within the ranges of 40 to 44 C and 12 to 20 C. In the hot-water bath muscle temperature was higher than the core temperature, and was lower than the core temperature in the cold-water experiments. Strong contractions

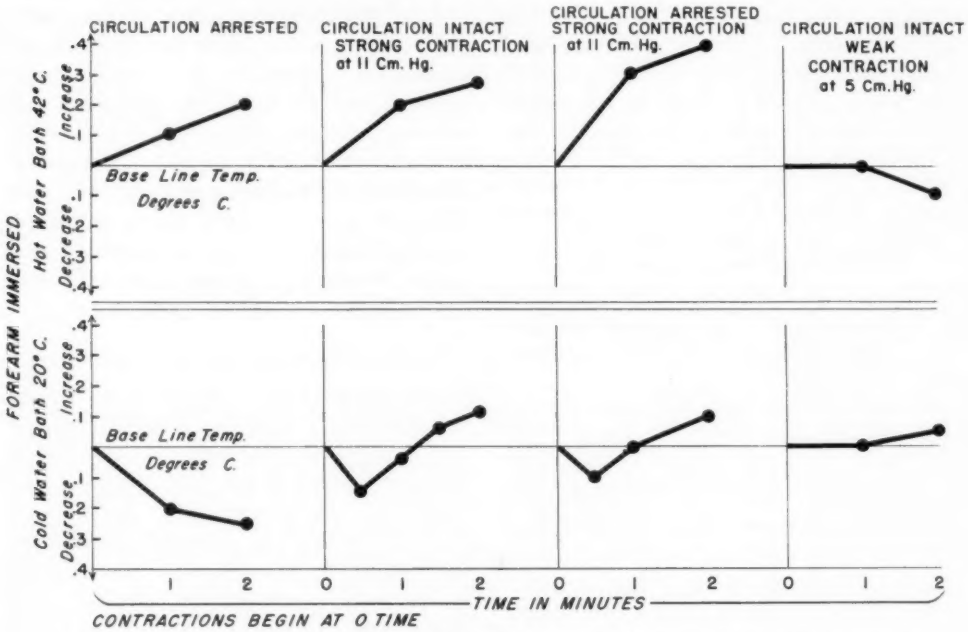

Fig. 5.—Initial muscle temperature changes during sustained contractions with forearm in cold- and in hot-water baths.

Comment.—Grant,[8] using a plethysmograph to determine forearm blood flow during rhythmic exercise, has demonstrated a similar progressive increase in blood flow between contractions and a relative diminution during the contraction itself.

Initial Skeletal Muscle Temperature Changes in Sustained Contractions with the Forearm in Hot- and Cold-Water Baths

In Figure 5 the alterations in the muscle temperature observed to occur within the first two minutes of sustained contractions performed in hot- and cold-water baths have were of 11-cm. strength, and the weak contractions were of 4 cm. strength.

In the hot-water-bath experiments arrest of the circulation allowed the muscle to gain heat. The greatest temperature elevation was noted when the heat produced by a strong contraction was added to the heat of muscle with its circulation occluded. It is inferred that the slight fall in temperature in the weak contraction was brought about by increased blood flow.

In the cold-water-bath experiments arrest of the circulation deprived the muscle of

blood-flow heat. The strong contractions decreased blood flow, as indicated by the temperature fall. A later rise in temperature probably represented heat from the contraction. The weak contraction produced a rise in temperature, presumably resulting from the heat of contraction and heat from the relative increase in blood flow.

Comment.—The basic assumption underlying these experiments is that increasing the blood supply to a part of the body at a temperature different from core temperature tends to bring the temperature of the part into equilibrium with core temperature.¶ These observations, and those of Barcroft and Miller,[7] afford evidence of the barrier to the muscle blood flow produced by sustained muscle contractions.

TABLE 2.—*Pain Threshold and Muscle Temperature with Circulation Intact*
(All Contractions at 11 cm. Hg)

Environmental Temperature	Average Muscle Temperature	Pain Threshold, Sec.
Water bath at 42 C.....	37.9 C	77
Room air at 26 C.....	35.8 C	57
Water bath at 20 C.....	32.4 C	33
Water bath at 15 C.....	26.0 C	No pain

INFLUENCE OF MUSCLE BLOOD FLOW AND VENOUS STASIS ON PAIN PRODUCTION IN SKELETAL MUSCLE

Influence of Blood Flow on Muscle Pain

With blood flow intact, 11-cm. contractions were performed with the forearm immersed in a hot- and in a cold-water bath. The temperature and the conditions were the same as those described in the preceding section. Control tests were done on the opposite arm, exposed at room temperature.

The results are tabulated in Table 2. In the hot water the average pain threshold was 77 seconds, with a range of 62 to 97 seconds. After 15 minutes' immersion in the cold-water bath, the average pain threshold was 33 seconds, with a range of 31 to 35 seconds. Pain threshold values, however, rose after longer periods of immersion in the cold-water bath, and after 30 minutes of immersion in a bath at 15 C no pain whatever was felt when the forearm was contracted.

Comment.—Other studies # have shown that immersion in a water bath at 45 C increases blood flow by three to five times the resting level. A water bath at 20 C reduces flow to less than one-half the resting value. The lack of pain during the sustained contraction performed after 30 minutes of immersion in the cold-water bath may be explained by the anesthesia of peripheral nerves which follows prolonged cooling.*

From the foregoing results one may infer that reducing muscle blood flow promotes the appearance of pain in the muscle, whereas increasing muscle blood flow delays the pain process. Kellgren † has reported observations in which short periods of vascular occlusion or cooling intensified the pain associated with various traumatic and infectious processes. In addition, he noted prolonged intense pain in conditions with deep hyperalgesia when the part was cooled.

Effect of Venous Stasis on Muscle Pain

The relationship of venous stasis to the development of pain in contracting muscle was evaluated in two subjects. Moderately intense muscle pain was produced by a sustained contraction performed while blood flow was occluded by a sphygmomanometer cuff inflated to 200 mm. Hg. The pressure in the sphygmomanometer cuff was then slowly released (Fig. 6). No change in pain intensity was noted until the arterial blood flow was reestablished, at approximately 120 mm. Hg. At that point a slight decrease in pain intensity occurred. Between pressures of 120 and 45 mm. Hg there developed progressive engorgement of the veins, during which period the pain persisted unchanged. Pain disappeared when cuff pressures between 55 and 35 mm. Hg were reached, at which time the veins began to empty. Venous distention alone was not productive of pain. This was demonstrated by repeating the experiments with the contraction omitted.

¶ References 10 and 11.

References 17 to 19.

* References 20 and 21.

† References 22 and 23.

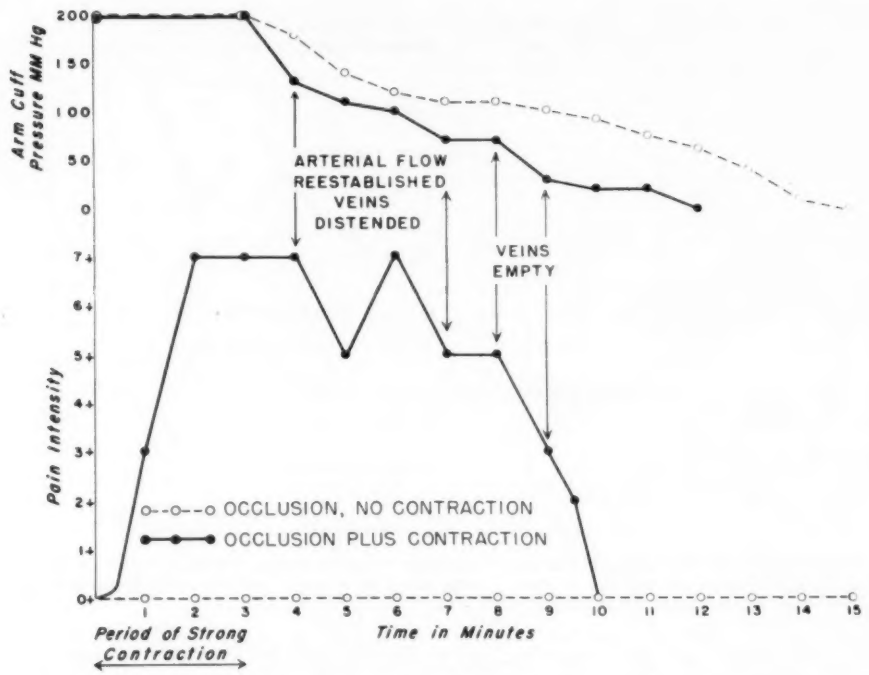

Fig. 6.—The relationship of venous stasis to the development of pain in contracting muscle.

Ten 11-cm., sustained contractions were performed with the sphygmomanometer at a pressure of 70 mm. Hg, a pressure which allows arterial blood to enter, but prevents venous blood from leaving, the arm. Pain threshold in these experiments averaged 35 seconds in one subject. The pain threshold in the same subject for the same strength contraction with the circulation unimpaired was 60 seconds.

Comment.—Venous return depends on the massaging effect of intermittently contracting muscles. Sustained contractions, on the contrary, impede blood flow and lead to venous stasis. Obstruction to either arterial or venous blood flow, then, promotes the appearance of pain in contracting muscle.

COMPARISON OF FATIGUE AND PAIN IN SKELETAL MUSCLE AND THEIR RELATION TO MUSCLE BLOOD FLOW

Strong forearm contractions were performed until pain was moderately severe and the contractions could no longer be maintained. Then, when the circulation was occluded, there was no diminution of either pain or fatigue.[24] These observations indicate that fatigue, at least under these conditions, is, like the stimulus for pain, a peripheral phenomenon.

In Figure 7 are compared blood flow, muscle temperature, pain threshold, and endurance changes during a sustained 11-cm. contraction held to endurance. The control pain threshold for the subject was 60 seconds, and the control endurance time was 160 seconds. The figures for the blood flow are adapted from the plethysmographic studies of forearm volume changes during sustained contractions reported by Grant.[8]

An endurance contraction was performed and was followed by a rest pause of specified duration. Then another endurance contraction was done. At no less than 20-minute intervals the two endurance contractions were repeated, each time with a slightly longer rest pause between contractions. The pain threshold and endurance time of the

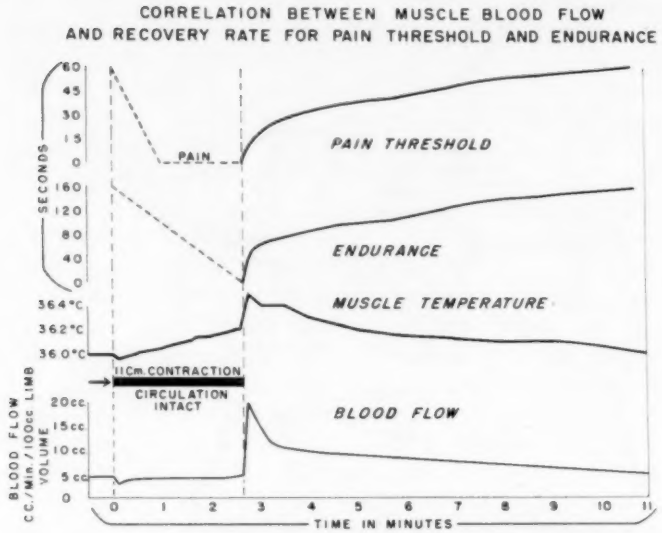

Fig. 7.—Comparison of pain threshold, endurance, forearm volume changes (blood flow), and muscle temperature during and following a sustained contraction held for maximum duration. Blood flow changes have been adapted from Grant.[8]

second contraction in each exercise are plotted in a manner to show the recovery of muscle from fatigue and pain induced by a strong contraction.

The close parallelism between postcontraction hyperemia and recovery curves of endurance and pain threshold is striking. Within the first 30 seconds of the recovery period—the period of maximum blood flow—the endurance and pain threshold have risen to 75 seconds and 25 seconds, respectively, or almost half the normal values.

Comment.—These data indicate that the postcontraction recovery periods of skeletal muscle from pain and from fatigue run a similar course and that the recovery rate is roughly proportional to the magnitude of blood flow.

SKELETAL MUSCLE ACTIVITY PATTERNS
VARIATIONS IN REST-PAUSE DURATION, PAIN THRESHOLD, AND ENDURANCE IN INTERMITTENT CONTRACTIONS

In the section on rhythmic contractions it was pointed out that the resting phase of an intermittent contraction brings about increased blood flow. In the following experiments (Fig. 8) are demonstrated the effects of changes in the length of the rest pause on the pain threshold and on endurance. All contractions were of 11-cm. strength.

It was possible to continue for 48 minutes an exercise consisting of 20-second contraction periods and rest pauses of 10 seconds. Toward the end of this period continuous tenderness and pain were present. The arm appeared and felt firm and swollen. In another experiment, reduction of the relaxation period to five seconds shortened the contraction endurance from 48 minutes to 6½ minutes. In the exercises with the shorter rest pauses the pain threshold and endurance decreased rapidly to the point where the contraction could no longer be held.

Comment.—The retention of fluid and electrolytes within the active muscles during and after prolonged intermittent contractions described by other investigators [25] may explain in part the swelling observed. When a standard contraction is repeated without an adequate intervening rest period, the pain in the second contraction comes on much sooner; and the shorter the rest period, the earlier the onset of pain in the succeeding contraction. This would indicate that cessa-

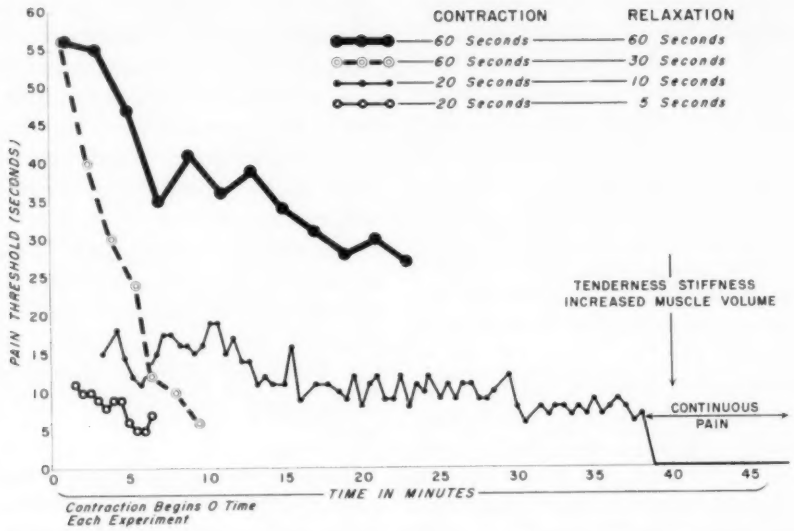

Fig. 8.—The relation of changes in rest-pause duration during intermittent contractions to pain threshold and endurance.

tion of contraction is accompanied by a diminution of Factor P concentration rather than by complete recovery of the muscle.

The spacing and duration of muscle relaxation pauses during contractions are important factors in muscle economy. Anerobic chemical reactions provide the muscle with energy for only short periods, whereas contractions in which rest pauses are sufficiently long to insure adequate blood flow and oxygenation provide the muscle aerobic energy sources for prolonged periods. Prolonged skeletal muscle activity requiring predominantly anaerobic mechanisms for contraction energy, i. e., contractions performed with brief or no rest pauses, is costly in terms of early fatigue and pain.

RECAPITULATION AND COMMENT

Skeletal muscle pain and tenderness predictably occur during sustained or prolonged intermittent muscle contractions. The threshold (time interval between start of contraction and onset of pain) and the intensity of the pain are directly related to the strength of the muscle contraction. With strong contractions the onset of pain occurs quickly and its intensity is high. With weaker contractions the onset of pain is delayed and its intensity relatively low. The fact that development of muscle fatigue parallels the genesis of pain precludes the possibility of a strong contraction, and hence high-intensity pain, continuing over long periods of time. Relaxation of the active muscles is accompanied by prompt disappearance of the pain. The tenderness of hyperalgesia which almost invariably accompanies the pain may persist, however, after pain has subsided.

The mechanisms involved in the pain process pertain to the circulatory and metabolic dynamics of skeletal muscle activity. The actual process of contraction, by obstructing mechanically the vessels supplying the muscles with blood, renders the muscle relatively ischemic for the duration of the contraction. The degree of ischemia, as determined by a variety of blood-flow experiments, is approximately proportional to the contraction strength, a strongly contracting muscle being almost completely ischemic. The increase in blood flow which accompanies muscle activity takes place predominantly during the periods of relaxation occurring between contractions. Thus, depending on the form, duration, and intensity of motor activity, the muscle may

be relatively ischemic over a long time interval. This prolonged state of anaerobic activity allows for the shift of electrolytes across the cell membrane or accumulation within the muscle of metabolic products which would otherwise have been dissipated in the presence of adequate blood flow. One may speculate that tissue damage [26] of an ordinarily reversible nature, such as, for example, the shift of potassium across the cell membrane during ischemia or contraction, may be the adequate stimulus for skeletal muscle pain.

Evidence for the nature of Factor P has accumulated from the work of Lewis, Perlow, and associates ‡ and our own. It has been shown that Factor P accumulates in ischemic muscle, the rate of production being much faster in contracting skeletal muscle. The process is rapidly reversible in the presence of fresh blood supply. The concentration of Factor P depends on the strength and duration of the contraction and the rate of blood flow. Agents suggested to be Factor P include anoxia,§ acid metabolites,‖ products of tissue injuries,¶ phosphoric acid,¶ histamine,[35] and potassium.#

The role of anoxia * in production of muscle pain is disputed. Kissin [31] reported significantly a lower pain threshold during muscle contractions performed by subjects breathing atmospheres of low oxygen tension. Pickering and Wayne [38] found a lower pain threshold in contracting muscle of anemic patients.

Lang [33] showed that the maximum depression in muscle pH, total carbon dioxide, and lactic acid occurred some time after resumption of blood flow following a contraction. It is unlikely, then, that these factors could account for muscle pain, since pain is maximum at the end of exercise and rapidly disappears with resumption of blood flow.

‡ References 27 to 29.

§ References 30 and 31.

‖ References 32 to 34.

¶ References 21 and 22.

References 36 and 37.

* References 29, 30, and 35.

Studies of intracellular and extracellular potassium shifts in relation to muscle blood flow, ischemia, and muscle contraction indicate that potassium has many of the properties of the postulated Factor P. Both exercise [16] and ischemia [39] have been found to bring about release of potassium from muscles.

The duration of stimulation and strength of muscle contraction are directly related to the amount of potassium loss from the muscle.[40] The rate with which potassium was lost from muscle according to other investigations paralleled the rate of blood flow.[41]

Injected intra-arterially, potassium provokes severe pain in skeletal muscle qualitatively similar to ischemic muscle pain.[37] Potassium shifts across the cell membrane during ischemia or contraction may also be implicated in the production of muscle fatigue. Recent evidence indicates that the site of fatigue is peripheral.[24] The fact that paresis occurs with either hypo- or hyperkalemia suggests disturbance of a common physiologic function. Several studies † have shown that the membrane potential of both nerve and muscle is determined by the ratio of potassium inside to potassium outside the fibers. Raising the intracellular potassium concentration, it was found, reduced the excitability and the membrane potential.[44] Intracellular and extracellular potassium are in constant interchange,[45] but energy is required to maintain the concentration gradient across the cell membrane.

In Addison's disease there is a high blood level of potassium and muscle weakness. Attacks of paralysis are associated with low blood potassium levels in familial periodic paralysis. Calhoun and associates ‡ found low cardiac muscle potassium in congestive heart failure and decreased skeletal muscle potassium in skeletal muscles which have been overworked.

† References 42 to 44.

‡ References 46 and 47.

SUMMARY

Pain and tenderness predictably occur during sustained and intermittent contractions of forearm skeletal muscles performed with circulation intact and are qualitatively identical with ischemic muscle pain.

Threshold and intensity of pain and endurance of contraction are directly related to the contraction strength. With a strong and sustained contraction they are of similar magnitude with circulation intact and with circulation occluded. With circulation intact, progressively weaker sustained contractions are associated with longer endurance, higher pain thresholds, and lower pain intensities than are observed in similar experiments with occluded circulation. In rhythmic exercises with intact blood flow endurance is greater, pain threshold higher, and pain intensity lower than in sustained contractions of similar strength.

Data from experiments in which muscle temperature was used as an index of blood flow indicate that tonically contracted muscles are relatively ischemic, the degree of ischemia being proportional to the contraction strength. Hyperemia follows strong contractions and occurs during the rest pauses of rhythmic exercises.

Return of the lowered muscle pain threshold to control resting levels parallels the rate of recovery from fatigue and is proportional to the magnitude of the postcontraction blood flow.

It is postulated that during the period of relative ischemia which accompanies contracting skeletal muscles there are produced noxious metabolites (Factor P of Lewis), capable of engendering pain. The accumulation of these substances in concentrations sufficient to exceed the pain threshold depends on the form, intensity, and duration of contraction.

The available evidence indicates that muscle potassium is the pain factor, or one of its important components.

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Irregular Fluctuation of Elevated Cerebrospinal Fluid Pressure

Such Fluctuations as a Measure of Dysfunction of Cerebrovascular Episodes, Pseudotumor Cerebri, and Head Injury

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In some patients with increased intracranial pressure there are irregular rapid fluctuations of the pressure. They can be found in the course of routine lumbar puncture in quiet (or sedated) patients by observing the pressure for a few minutes. These pressure changes have been mentioned, briefly and without explanation, in reports of cases of severe head injury,* brain tumor,† cerebral pseudotumor,‡ and acute cerebral vascular disease.[6] The purpose of the present study is to seek the origin and significance of these fluctuations.

THE CEREBROSPINAL DURA AS AN ONCOMETER

Under pressures compatible with life, the cerebrospinal dura is essentially not distensible.[7] It contains the central nervous system, cerebrospinal fluid (CSF), and blood, all of which are practically incompressible. The CSF pressure is the sum of the partial tensions exerted by neural tissue, CSF, and intradural blood. The sudden rises and falls in pressure which are the subject of this study are not likely to be caused by changes in volume of neural tissue (that is, cerebral edema) or of CSF.[8] On the contrary, they could readily result from changes in volume of intradural blood vessels—arterial or venous or both.

Since 1887 § the dura has been used as the chamber of an oncometer or plethysmograph to determine changes in the volume of intradural blood. The sensitivity of this method of determining rapid changes in intradural blood volume may be impaired by low or normal CSF pressure, leakage around the needle, and/or the narrow bore of the lumbar puncture needle.

When the CSF pressure is normal (80 to 180 mm. of water), the spinal dura and cerebral veins are slack.‖ Under these conditions rapid changes of intradural blood volume will be partly absorbed by changes in volume of the cerebral veins and in distention of spinal dura. In other words, the CSF pressure changes will be damped. The dura, however, can be made a more sensitive oncometer either by introducing a few cubic centimeters of saline or Ringer's solution through the spinal needle or by elevating the patient's head and trunk in order to raise the CSF pressure to a level above 200 mm.

Occasionally spinal fluid will leak around the site of dural puncture into the epidural space.[12] Such a condition is indicated by

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† References 1, 2, and 3.

‡ References 4 and 5.

§ Falkenheim and Naunyn,[9] cited by Hill, L.: The Physiology and Pathology of the Cerebral Circulation: An Experimental Research, London, J. & A. Churchill, Ltd., 1896.

‖ References 10 and 11.

a progressive drop in mean CSF pressure in the course of the observations (Fig. 1). Because of this possibility, one should record only rises, rather than falls, of CSF pressure in determining fluctuations ascribed to changes in the intradural blood volume (and cerebral vascular tonus).

O'Connell [13] demonstrated the damping effect of narrow bore of a lumbar puncture needle in demonstrating rapid changes of CSF pressure. For example, a 100 mm. shift in pressure in three-second cycles was recorded as a change of only 2-3 mm. in a manometer attached to a lumbar puncture needle. Nevertheless, the fluctuations of

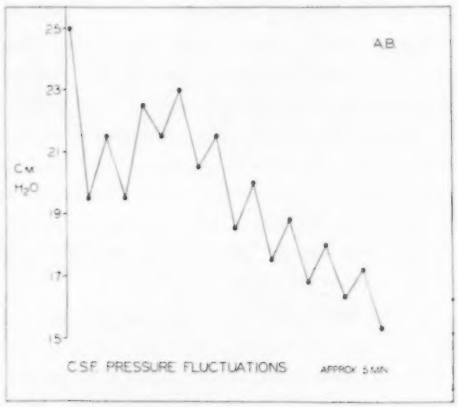

Fig. 1 (Case 1; age 66).—Fluctuations of CSF pressure, three days after stroke. The gradually descending curve indicates a leak of cerebrospinal fluid around the needle into the epidural space.

CSF pressure which are the subject of this study are so great that they cause observable changes of over 20 mm. under such circumstances, often in a fraction of a second. The true changes of pressure are so great, therefore, that the routine lumbar puncture needle of 18 g or 20 g is adequate for present purposes.

Any rise in intradural venous volume, such as that produced by coughing, jugular compression, or abdominal compression, will be followed by a rise in mean CSF pressure. Therefore, one disregards sudden CSF pressure rises associated with such obvious sources of error.

METHOD AND OBSERVATIONS

In the course of routine lumbar puncture with an 18- or a 20-gauge needle and the usual glass vertical, stand-pipe manometer of the Fleischer type, the pressure was observed by Dr. J. P. Schaerer or me for five minutes. The patient was lying on his side, with head in line with his body and no pressure on the neck or abdomen. We called off pressure readings to an assistant. In the case of fluctuating pressures, we tried to record high and low fluid levels. These levels were reached in from less than a second to over 15 seconds. The fluid often rose (or fell) and paused for a moment—then continued on its course. If the patient strained, moved, coughed, or spoke vigorously, no reading was recorded. All patients were awake and cooperative except for three, who had been restless, and therefore had been put to sleep by intravenous amobarbital (Amytal) sodium or thiopental (Pentothal).

These observations were made in 44 successive appropriate cases in a neurosurgical service in the past two years. If there was fluctuation of the CSF pressure of at least 20 mm. (readings being recorded only of a rise in pressure, to avoid the error caused by epidural leakage), the reading was considered positive. There were 21 positive cases, to which I have added 3 cases of pseudotumor cerebri, all positive, from former years. There were 23 negative cases, or controls.

Negative Cases (Controls).—There were 23 cases with spontaneous fluctuations of less than 20 mm. In all but four cases the original pressure was less than 200 mm. In 12 of the cases with low or normal pressure, isotonic saline solution was added in increments of 2 cc. to raise the pressure to a level over 200 mm. and thus distend the dura, making it more sensitive as an oncometer. The pressure was raised to over 300 mm. in four of these cases and to 520 mm. in a fifth. However, in only 1 of these 12 cases in which pressure was raised, and in 1 in which the original pressure was 285 mm., did there result a fluctuation of over 20 mm. These cases are described in the third paragraph to follow.

The final clinical diagnoses were arteriovenous malformation (without recent hemorrhage), acute cerebral vascular episode (four cases), colloid cyst of the third ventricle, acoustic nerve tumor, retrobulbar neuritis, psychoneurosis (four cases), post-

operative subdural hematoma with cerebral collapse, cerebral atrophy (two cases), cerebellar atrophy, amyotrophic lateral sclerosis, traumatic cerebral edema in a child, multiple sclerosis (two cases), thrombosis of the internal carotid artery, meningioma, and neuronitis.

In one case of nontraumatic subarachnoid hemorrhage in a hypertensive adult, the original CSF pressure was over 600 mm. of water at the time the patient's blood pressure was 260/120 mm. Hg. The systemic blood pressure was lowered to 65/10 by an intravenous injection of hexamethonium. At the same time the spinal fluid pressure fell *pari passu* to 400 mm. of water. At no time was there any appreciable fluctuation of the spinal fluid pressure. The patient died a few minutes after this procedure. Autopsy disclosed intracerebral and intraventricular hemorrhage, as well as marked herniation of the cerebellar tonsils into the foramen magnum. It is probable that this cerebellar impaction prevented transmittal of any rapid fluctuation of intracranial (or CSF) pressure into the spinal canal.

Among the controls, where the CSF pressure fluctuations were less than 20 mm., there were three cases of acute cerebral vascular disorder. These readings were made on the 9th, 15th, and 30th days, respectively, after the stroke. In one case, in which the lumbar puncture was made on the 9th day, the pressure fluctuated between 280 and 290 mm. When saline solution was introduced into the spinal canal, the pressure then fluctuated between 400 and 446 mm. In the second case, in which lumbar puncture was made on the 15th day after the stroke, the initial CSF pressure was steady at 92 mm. When saline solution was added, the pressure fluctuated between 270 and 300 mm. In the last case, in which the pressure was measured 30 days after the stroke, the pressure was steady at 260 mm.

Positive Cases.—There were 21 positive cases—that is, spontaneous fluctuation of over 20 mm. of CSF pressure—observed in the past two years. I have added three cases of pseudotumor cerebri observed previously. In all of these 24 cases the original pressure was over 180 mm. of water.

In five cases of the present series in which marked fluctuations were observed at the initial reading (average 53 mm.), smaller fluctuations were found at lower pressures after 10 cc. was removed (average 23 mm.) (Figs. 3, 4, and 5). On the other hand, in three cases greater fluctuations were observed at higher pressures produced by injection of a few cubic centimeters of saline solution. These observations indicate that the cerebrospinal dura is a more sensitive oncometer at higher pressures (generally between 200 and 400 mm. of water) than at lower (generally below 200 mm.).

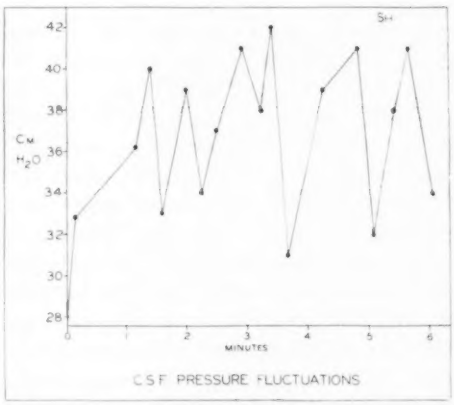

Fig. 2 (Case 2; age 27).—Fluctuations of CSF pressure. The pressure rose from 310 to 410 mm., a range of 100 mm. The patient was still unconscious at the time of this examination, three days after severe blunt head injury. At a later examination, 17 days after the injury, the range of fluctuations of CSF pressure was less than 5 mm., even when the patient's head and shoulders were elevated, so that the mean pressure was over 300 mm.

These cases, and some from the literature, will be considered under the following clinical headings: trauma (2 cases), pseudotumor cerebri (3 cases), cerebral vascular disorders (13 cases), and miscellaneous disorders (6 cases including 2 brain tumors).

Trauma: In 1945 it was suggested [14] that in a blunt head injury traction on the carotid artery either in the neck or in the

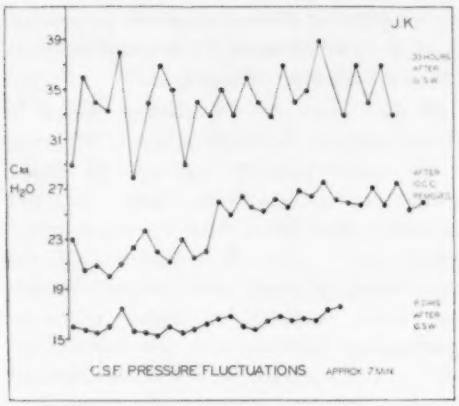

Fig. 3 (Case 3; age 15).—Fluctuations of CSF pressure, in a case of gunshot wound of the face and neck, with cerebral symptoms ascribed to spasm of the carotid artery, described in the text.

subarachnoid space resulted in arterial spasm, which could produce ischemia of the brain. Löhr [15] showed constriction and increased resistance of the cerebral arteries angiographically in cases of cerebral contusion. Grant ¶ and Bragdon [2] noted unexplained major oscillations in spinal fluid pressure in patients following acute head injury. The latter noted that these oscillations occurred only when the CSF pressure was more than 20 mm. of mercury and published graphs of them. I have confirmed these CSF observations in a number of cases of cerebral contusion (not included in the present series except for Figure 2). When the head of the bed was elevated, not only mean CSF pressure but also range of fluctuation increased in some cases. Furthermore, as time passed, in these traumatic cases, both mean CSF pressure and range of fluctuation tended to become lower.

One case of the present series was a 15-year-old youth who suffered a gunshot wound of the face and neck. The wound of entry was at the lower edge of the right orbit and the wound of exit 4 cm. to the right of the interspace between the spinous processes of the third and fourth cervical vertebrae. There were immediate unconsciousness, left hemiplegia, and aphasia; the boy was left-handed. There was no demonstrable fracture, except of the maxilla. Thirty-three hours after he was wounded the CSF pressure fluctuated between 200 and 278 mm. of water. Eight days after injury the initial pressure of spinal fluid fluctuated between 156 and 176 mm. (Fig. 3). Two months after onset the patient had made a complete clinical recovery. His spinal fluid pressure was 168 mm. of water, and it did not fluctuate. When the patient sat up, his CSF pressure was 484 mm. of water, with fluctuations of less than 2 mm. This case was considered one of traumatic spasm

¶ Reference 1. Grant, F. C., in discussion on Bragdon.[2]

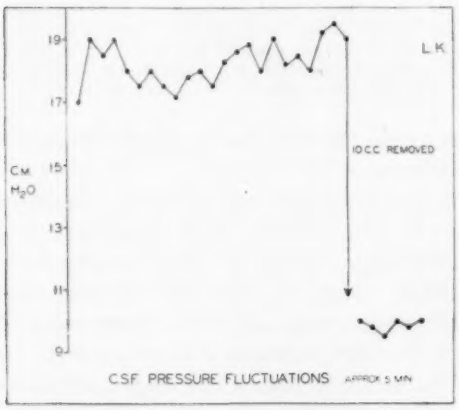

Fig. 4 (Case 4; age 71).—Fluctuations of CSF pressure, 16 hours after cerebral stroke.

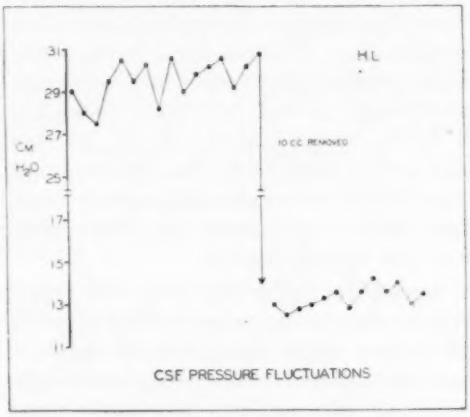

Fig. 5 (Case 5; age 62).—Fluctuations of CSF pressure, 18 hours after cerebral stroke.

of the internal carotid artery in the neck, which extended to its cerebral branches.[14]

Comment. These data suggest that excessive cerebral vasoactivity is often present following severe craniocervical trauma. It tends to diminish with time. It may have produced enough cerebral ischemia at the time of the original trauma to result in cerebral dysfunction.

Pseudotumor Cerebri: In 1931 Egas Moniz [16] described a series of cases in which there was papilledema of unknown cause. Arteriograms failed intermittently to reveal the bifurcation of the internal carotid artery. On other occasions the arteriograms were normal. I interpret these observations as indicating pseudospasm of the internal carotid artery or its branches.[17]

In 1937 Dandy [8] reported 22 cases of pseudotumor cerebri. These cases were marked by increased intracranial pressure of varying intensity, which lasted for months or years. He emphasized that the degree of intracranial pressure varied extremely over a period of a few minutes. He thought that these rapid alterations of pressure could hardly be explained except by "variations in the vascular bed."

Recently thrombosis of the superior longitudinal sinus has been found in cases of pseudotumor cerebri.# However, in at least two of these cases carotid arterial thrombosis was shown angiographically.* It is not possible to say which came first, the arterial or the venous thrombosis.[20]

In my three cases of pseudotumor cerebri there were marked spontaneous fluctuations of the cerebrospinal fluid pressure: In the first case it fluctuated 190 mm. (from 410 to 600 mm.) of water, and as much as 60 mm. in four seconds. In the second case the pressure alternated 40 mm. (from 246 to 286 mm. of water). In the third case the CSF pressure (with patient horizontal) had a range of 60 mm. (from 320 to 380 mm. of water); with the patient sitting up, there were variations of 80 mm. (from 70 to 150 mm. of water) within two seconds.

Angiography in these three patients revealed pseudospasm in one † and normal arterial filling in the other two. These patients have been followed for 4, 13, and 6 years, respectively, with gradual subsidence of the papilledema. All are now in good health. Gardner has observed similar marked, apparently spontaneous, fluctuations of CSF pressure in cases of pseudotumor cerebri.‡

Comment. These data tend to confirm Dandy's opinion that there is disordered or excessive cerebral vasoactivity in some cases of pseudotumor cerebri.

Cerebral Vascular Disorders: In the present series there were 14 cases of sudden cerebrovascular dysfunction. Of these, there were 10 of hemiparesis, suggestive of a supratentorial lesion, and 4 in which there was disorder of external ocular movements, suggestive of a brain stem lesion. In 10 cases there was blood in the cerebrospinal fluid at the time of the original puncture. Hypertension, at least intermittent, was known in 11 of these cases.

Angiograms were made in six of these cases and revealed definite evidence of arterial spasm [17] in three cases and evidence suggestive of spasm in two. In the sixth case there was occlusion indicative of thrombosis of the internal carotid artery near its origin; hence the cerebral arteries were not visualized.

Fluctuation in the initial cerebrospinal fluid pressure was 20 mm. or more in 10 of these cases, and they, therefore, belong in the positive series (Figs. 4 and 5). The higher fluctuations were found when the puncture was made within a few days of the stroke, especially within the first 24 hours. The readings in the positive cases were all made within 25 days of the stroke except for one, which was made four months later. Of the four negative cases, as mentioned previously, two displayed fluctuations

References 18 and 19.

* References 19 and 20.

† References 17 and 21.

‡ References 4 and 5.

of CSF pressure exceeding 20 mm. when the mean CSF pressure was raised.

Comment. The observation of fluctuations in CSF pressure soon after an acute cerebrovascular disorder (stroke) confirms the excessive cerebral vasoactivity which previously had been recognized clinically,[22] angiographically,§ electroencephalographically,[24] neuropathologically,‖ and experimentally.¶

Miscellaneous Disorders, Including Brain Tumors: Occasionally extreme fluctuation of CSF pressure has been described in the presence of a brain tumor. Grant's patient,[1] with craniopharyngioma, had unexplained brief rises of CSF pressure of from 150 to 400 mm. of water while apparently physically and mentally composed. Bragdon's patient,[2] with a brain tumor, had a basic CSF pressure of 50 mm. of mercury (680 mm. of water), which occasionally spontaneously exceeded 90 mm. of mercury (1224 mm. of water). Gardner and others [3] described similar unexplained fluctuations of CSF pressure on two occasions in a patient with an acoustic nerve tumor. In the present series there were two cases of brain tumor in which the CSF pressure fluctuated more than 20 mm. of water.

Other cases with more than 20 mm. of fluctuation of CSF pressure included one patient with cerebral atrophy and epilepsy, one with multiple sclerosis, one with hydrocephalus and aqueductal stenosis, and one with duodenal ulcer.

Comment. Apparently, increased cerebral vasoactivity, while producing excessive fluctuations of CSF pressure, may be essentially asymptomatic and nonpathogenic.

COMMENT

In certain pharmacodynamic situations there is a parallel relationship between CSF arterial pulsations and mean CSF pressure. For example, both increase after the intravenous injection of histamine # or the inhalation of CO_2. Guillaume and Janny [33] published such a curve in association with flushing of the face. In these situations there is a rise in the volume of intradural arterial (probably arteriolar) blood from each heart beat. These changes probably also occur soon after some epileptic seizures in which both the pial arteries and the entire cerebral hemisphere are seen to pulsate excessively.[34] On the contrary, both the amplitude of CSF arterial pulsation and the mean CSF pressure during attacks of migraine were diminished by the injection of ergotamine.[30] These oscillations of CSF pressure are rhythmical and indicate generalized or synchronous cerebral arterial activity.

Guillaume and Janny recorded intraventricular pressure for long periods.[33] They observed large spontaneous oscillations in pressure, which occurred with a frequency of 0.5 to 12 per minute (that is, with cycles of 120 to 5 seconds) in sporadic outbursts, lasting from minutes to hours. These changes in pressure were ascribed to "autonomous vasomotricity" and were not associated with any variation in the clinical state of the patient. Vujić [35] observed fluctuations in lumbar CSF pressure during sleep in 16 of 103 patients. These pressure changes lasted 20 to 40 seconds and were from 10 to 90 mm. high; in these patients when awake the fluctuations did not exceed 20 mm. of water. Others [36] have essentially confirmed these observations.

Fluctuations in CSF pressure indicate changes in total intradural blood volume, that is, an algebraic sum of increases and decreases of blood volume in different topographic regions of the brain. In other words, small changes tend to cancel each other; only net differences in intradural blood volume are reflected in alterations of CSF pressure. The fluctuations of CSF pressure described in this paper are arrhythmic or irregular and probably indicate disorganized or nonsynchronous cerebral vasoactivity.

This dysfunction of cerebrovascular (probably more arterial than venous) tonus can be ascribed to traction on the vessels due to trauma,[14] or to extreme systemic arterial

§ References 6, 17, and 23.
‖ References 25 to 27.
¶ References 28 and 29.
# References 30 to 32.

hypertension,[29] or to unknown causes (perhaps systemic and/or local humoral agents). Folkow,[37] has demonstrated experimentally rhythmic changes of tone after release of arterial obstruction.

This vascular dysfunction has been found primarily in patients who are recovering from an acute cerebrovascular episode (stroke) or severe head injury in which there may have been originally severe arterial spasm with ischemia (which can produce an array of disorders in the blood vessels and parenchyma of the nervous system). These data are consistent with clinical angiographic and other data indicative of arterial spastic tendencies in these disorders (see previous "Comments").

Objections.—It may be objected that the fluctuations of CSF pressure merely reflect alterations in systemic blood pressure. Furthermore, according to Ryder and others,[38] the CSF arterial pulsation varies concomitantly with the irregular arterial pulsations of auricular fibrillations and extrasystoles or with occlusion of both carotid arteries.[32] On the other hand, in the cases under consideration here, there was no demonstrable change in arterial pressure whenever a study was made. This was done in the present series in the three cases of pseudotumor cerebri, in several cases of cerebrovascular disorder, and in the case of the boy with the gunshot wound of the face and neck. Furthermore, the graphs of Grant,[1] Bragdon,[2] and Guillaume and Janny[33] show steady systemic arterial blood pressure while the CSF pressure was fluctuating excessively.

It is conceivable that the CSF pressure fluctuations resulted from intermittent venous obstruction.[39] However, in none of the reported cases was there heart failure or dilatation of the veins of the neck. Furthermore, readings were obtained only from quiet, cooperative patients (in three of whom anesthesia was employed). If the patient coughed, moved, or talked, readings were disregarded. Finally, these fluctuations in pressure might be related to changes in production or absorption of the cerebrospinal fluid or of cerebral edema. It does not seem reasonable[8] to expect such changes to be as rapid as the alterations in pressure indicate. However, even if any of these changes in CSF volume did occur so rapidly, they would be intimately related to vascular activity.

SUMMARY AND CONCLUSIONS

In some patients with increased intracranial pressure there are irregular, rapid fluctuations of the pressure. These fluctuations are seen in the course of routine lumbar puncture in quiet (or sedated) patients by observing the pressure for a few minutes. In 21 of 44 successive neurologic cases (37 with naturally or artificially elevated CSF pressure) there were such irregular fluctuations of at least 20 mm. of water, lasting from less than a second to more than 15 seconds. These changes were present commonly in patients with pseudotumor cerebri or in those recovering from recent head injuries or cerebrovascular disorders (strokes). For example, of 14 cases of recent cerebral stroke, there was fluctuation of CSF pressure 20 mm. or more in 10, and in 2 additional cases when the mean CSF pressure was raised to 200 mm. of water.

When mean cerebrospinal fluid pressure is elevated to a level above 200 mm. of water, whether by trauma or other disorder, by the introduction of isotonic saline or Ringer's solution, or by tilting the patient so that his head and trunk are elevated, the cerebrospinal dura acts as an oncometer. Then rapid fluctuations of pressure, observable on lumbar puncture, indicate changes in the total amount of blood within the central nervous system. Such changes usually result from excessive changes in tonus and caliber of cerebral blood vessels. This exaggerated cerebral vasoactivity is most commonly found in patients a day or two after severe head injury or cerebral stroke. At these times it is usually neither pathogenic nor symptomatic, but seems to indicate partial recovery from severe cerebroarterial constriction, which had been present at the onset of the lesion.

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The Psychophysics of Communication

III. Discriminatory Awareness in Stutterers and Its Measurement by the Critical Flicker Fusion Threshold

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That consciousness undergoes a severe disturbance in the stutterer during his efforts at communication has been noted in a previous study in this series (Lovett Doust and Douglass [5]). In this study an account was given of the introspections by the stutterer during his attempts to speak and of the clinical observations made of his state of mind at this time. In addition, it was noted that consciousness may be conveniently thought of in terms of a number of "parameters of awareness" and that certain of these parameters are susceptible to objective measurement by psychophysiologic monitors which vary predictably and in temporal relationship with them. Singled out for principal exemplification in that article were the changes undergone in the parameters of attentive and emotional (visceral) awareness during four phases of stuttered speech, as monitored by the oximeter and the cardiotachometer.

But it is not solely during their efforts to speak that stutterers reveal defects of consciousness; they are singularly constricted, it would seem, in their capacity for perception, concept formation (Lovett Doust and Webb [6]), conative drive, and other aspects of the communication process outlined elsewhere (Lovett Doust and Douglass [5]). A recently reported investigation of 100 adult male stutterers (Williams,[10] 1954) threw some of these impressions into sharp relief. Everything was "all right" for the stutterer, it was found, save his stutter. The patients were found to be unobservant of other people, forgetful even of their own histories, and with an amnesia for their childhood "extending up to the 11th year in some cases."

The present paper reports a study designed to quantify that aspect of consciousness underlying many of the above personality features of stutterers, i. e., the parameter of discriminatory awareness; and it introduces a technique enabling such measurments to be made.

CRITICAL FLICKER FUSION THRESHOLD (CFF) IN RELATION TO CONSCIOUSNESS

"Ability to discriminate" was separated out by Miller [7] (1942) as one of 16 definitions of consciousness, and discriminatory awareness refers specifically to that aspect of consciousness concerned with ability to differentiate between events occurring in the environment of the subject. Such a construct may conveniently be formalized by setting up a model in which events are deliberately presented to the subject in a regularly recurring sequence and the limits of his capacity to discriminate between them ascertained. Exemplification for such a model already exists in the critical flicker fusion threshold (CFF), on which a vast amount of work has already been accomplished (Landis,[2] 1953). Determination of the CFF includes the presentation to the subject, under a number of standardized conditions, of a flickering light stimulus: "The threshold point where intermittent illumination appears to fuse or an apparently steady light first appears to flicker is commonly designated as the critical flicker-fusion threshold or the CFF, and is usually expressed in cycles per second" (Landis and

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Hamwi,[4] 1954). The procedure is a simple one; the determinants of the threshold have been exhaustively investigated (e. g., Landis,[3] 1954); it is readily reproducible, can be repeated ad libitum, and may be employed, therefore, both on longitudinally studied and on cross-sectional population samples, and it has, as we have pointed out, a distinct and useful relationship to a specific parameter of awareness.

PROCEDURE

Two populations were sampled: one, a healthy, fluent, control group composed of 51 male and 80 female undergraduates from the faculties of arts, science, and laws, and the departments of social science, nursing, and physical education; the other, a group of 37 male and 9 female stutterers who had presented themselves for treatment at the speech pathology clinic of Toronto Psychiatric Hospital, and who were referred to us for psychophysiologic investigation by Mr. E. Douglass. The ages of the fluent group ranged from 17 to 43 years, with a mean age of 21.21 years (σ=3.219), and those of the stutterers from 11 to 53 years, with a mean of 25.65 years (σ=8.887). All subjects of both groups were mentally and physically healthy save for the symptom of speech difficulty in the stuttering sample.

The CFF thresholds were determined in identical fashion for the two groups. Tests were made individually in a semidarkened, quiet room with the subject seated 6 ft. away from a General Radio stroboscope (Strobotac), suitably masked to provide a circular white-light patch 1 in. in diameter. The subject was instructed in what was required of him, and two demonstrations were provided during the period of instruction of how the appearance of the patch could change from that of a flickering light to that of a continuous one, and vice versa, by changing the rate of flicker. Two runs were then made, care being taken to keep the slow rotation of the stroboscope dial at a constant speed, and the flicker rates at which the light first appeared intermittent and at which it first appeared continuous were determined. The CFF was taken to be the mean of these two readings, the difference of each reading from this mean being the deviation about it. In no case were readings taken before the subject fully understood what was required of him.

TABLE 1.—*Mean Critical Flicker Fusion Thresholds for Stutterers and for Fluent Controls*

Group	N	Mean CFF, cps	σ	Test of Significance
Fluent controls..	131	41.125	3.229	$t = 6.182$
Stutterers	46	36.087	7.398	$d.f. = 175$
				$P < 0.001$

TABLE 2.—*Mean Critical Flicker Fusion Threshold Deviations for Stutterers and for Fluent Controls*

Group	N	Mean CFF Deviation, cps	σ	Test of Significance
Fluent controls...	131	4.498	8.474	$t = 1.479$
Stutterers	46	2.609	1.480	P is N.S.

RESULTS

Table 1 shows that the mean CFF of the fluent (control) group (at 41 cps) is significantly higher than that of the stutterers (at 36 cps). Table 2 shows that the spread of the readings about the means is similar in these two groups.

Before these results may be taken unequivocally to support a lessened discriminatory awareness in stutterers however, it is necessary to consider whether other possible variables may be acting to interfere with these apparently clear-cut findings. Landis[3] has critically reviewed those physiological determinants of the CFF which appear to bear significantly on the results. When these factors are taken in order, it is obvious that those of intensity and luminance of the patch, area, light and dark adaptation and surround, duration of exposure, color, wave form, and light-dark ratio may be discounted, since the conditions of testing were identical for all subjects in the two groups. The slight difference often found between ascending and descending thresholds was counteracted by determining both these threshold values and expressing the result as the mean plus or minus deviations from it (Tables 1 and 2). Only the possibly critical factor of age remains.

Misiak[8] (1951) plotted the results of CFF threshold determinations for 319 subjects against their ages and found that the CFF fell progressively between 20 and 90 years. The mean age of our control group was 4.4 years less than that of the stutterers, and its range was less restricted. A t-test showed that the two samples differed significantly in regard to this age factor (t=6.022; σ=4.877; $P<0.001$), and it was deemed necessary to prove whether or no it was acting as an interfering variable in these results. A Pearson product moment

correlation coefficient determination was, accordingly, carried out on the combined groups. With $N=177$, r was found to be -0.153, and it was concluded that no significant relationship existed between age and the CFF with respect to the two populations investigated.

The final statistical procedure carried out was to ascertain whether a sex difference exists for the CFF of the control group. Tables 3 and 4 indicate that sex for our sample is not a differentiating variable, either for the CFF itself or for the deviation about its mean.

TABLE 3.—*Sex Influence on Critical Flicker Fusion Threshold in Fluent Controls*

Control Group	N	Mean CFF, cps	σ	Test of Significance
Males	51	41.698	4.119	$t = 1.306$
Females	80	40.076	8.336	P is N.S.
Total	131	41.125	3.229	

TABLE 4.—*Sex Influence in Critical Flicker Fusion Threshold in Stutterers*

Control Group	N	Mean CFF (cps) Deviation	σ	Test of Significance
Males	51	4.495	3.201	$t<1$
Females	80	4.498	2.570	P is N.S.

COMMENT

It would seem more than likely that stuttering exists on a neurogenic basis of some sort (Strauss,[9] 1954; Lovett Doust and Webb [6]), despite the flood of psychodynamic literature concerning it. The CFF is certainly a sensitive indicator of neurological efficiency (Landis,[1] 1951), and it is not surprising to find its threshold impaired in a typical sample of stutterers. It is, however, perhaps even more interesting to speculate on the relationship of communication, consciousness, and the CFF and the nature of the dysplasia existing between each of these variables in the stutterer. If each is correlated with the other, and if discriminatory awareness is impaired outside the expressive end of the communication spectrum, then it is probable that more than a single aspect of the process of thought may be affected. Evidence that this is so will be presented elsewhere.

SUMMARY

Critical flicker fusion threshold (CFF) is a valid method for measuring the parameter of discriminatory awareness.

The CFF was measured in 131 healthy, fluent, control subjects and in 46 stutterers and was found to be significantly depressed in the latter group. Conditions of testing were identical; the possible influence of age and sex was insignificant.

The interrelationship of the communication process as an aspect of thinking, of the discriminatory component of consciousness, and of the neurological implications of the CFF is discussed.

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Functional Localization in the Cerebellum

II. Somatotopic Organization in Cortex and Nuclei

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A new concept of the organization of the cerebellum into longitudinal, corticonuclear zones has been formulated (Chambers and Sprague [14]) on the basis of anatomical studies of Jansen and Brodal * and on our own physiological observations.† This concept stresses the importance of localization in the efferent corticonuclear projections, rather than the distribution of afferent fibers in the cerebellar cortex, in the interpretation of the results obtained by stimulation and ablation. Three bilaterally symmetrical zones have been defined in the cat (Fig. 1): (*a*) Each medial zone (vermal cortex and fastigial nucleus) regulates the tone, posture, locomotion, and equilibrium of the entire body; (*b*) each intermediate zone (paravermal cortex and nucleus interpositus) regulates the spatially organized and skilled movements and the tone and posture associated with these movements of the ipsilateral limbs, and (c) each lateral zone (hemispherical cortex and dentate nucleus) is involved in the same skilled and spatially organized movements of the ipsilateral limbs, without any apparent regulation of their posture and tone. The fact that the symptoms following lesions in the intermediate zone (nucleus interpositus) are indistinguishable from those obtained by pyramidal section, while those following vermal lesions are just as clearly extrapyramidal, has previously been pointed out and discussed (Chambers and Sprague [14]). The present communication is chiefly concerned with (1) the nature of the function of the lateral zone, (2) the problem of somatotopic localization of function within these zones, and (3) a critical comparison of the concept of "lobular," as opposed to "zonal," organization of the cerebellum.

The zonal concept of cerebellar organization stated in this and in previous publications revives an earlier hypothesis (of longitudinal subdivisions into vermis and lateral lobes) suggested in the works of Edinger [18] (1909), Comolli [15] (1910), Tilney [55] (1923), and Brun [11] (1925). Because this point of view is in marked contrast to the concept of lobular organization most widely accepted today, the evidence used to support the current lobular organization will be examined at some length and reevaluated.

The lobular theory states that the cerebellum is functionally organized, by transverse fissures, into four lobes (anterior, middle, posterior, and flocculonodular). It has its chief foundations in the comparative anatomical work of Bolk [7] (1906) and Elliot Smith [50] (1902), the embryological studies of Ingvar [26] (1923) and Larsell [32] (1937), and the experiments of van Rijnberk [45] (1904), Pagano [41] (1904), Rothmann [44] (1913), Fulton and Dow [20] (1937), and Dow [17] (1942). The arguments supporting a fundamental lobular organization have rested upon several lines of evidence: (*a*) the constancy of the fissure pattern in a large series of vertebrates (reviewed by Larsell [32]); (*b*) the relation of the fissure pattern and the relative development of the lobes to the size of muscle masses and the type of motor activity (reviewed by Ariëns Kappers, Huber, and

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* References 29 and 30.

† References 52, 53, and 54.

Crosby [6]) and Jansen [27]; (*c*) the distribution of the terminals of the afferent tracts in various lobes of the cerebellum (reviewed by Dow [17]), and (*d*) experimental ablations and stimulations (reviewed by Fulton and Dow,[20] Dow,[17] and Carrea and Mettler [12]).

The extensive series of papers by Larsell shows that a common pattern of development of the cerebellar cortex is present throughout the vertebrates. He emphasized the fundamental division of the cerebellum by means of the posterolateral fissure into a flocculonodular lobe and a corpus cerebelli. The corpus cerebelli he divided into anterior and posterior lobes by the primary fissure, and the posterior lobe was further divided by the secondary (prepyramidal) fissure. The flocculonodulus was called archicerebellum; the anterior lobe, pyramis-uvula, and paraflocculus were called paleocerebellum, and the ansoparamedian lobe (middle lobe of Ingvar) was termed neocerebellum.

Larsell's work has extended and clarified comparative anatomical studies of the cerebellar lobes and lobules and has made possible a basis for an attempt to relate these to specific functions and body parts. The physiological significance of these divisions is, however, ultimately dependent upon the specificity of their fiber connections, and of their functions as revealed by ablation and stimulation. The strongest support of the concept of lobular organization is the localization of vestibular function in the flocculonodular lobe (Dow [17]). This interpretation has been discussed recently (Chambers and Sprague [14]) on the basis of work in cats. The symptoms of unilateral or bilateral lesions in the vermal cortex of the centralis, culmen, and simplex and/or the rostral fastigial nucleus are strikingly similar to such ablations of the nodulus and uvula. In both, disturbances of posture, gait, and equilibrium of the whole body are found; we believe this fundamental similarity is more significant than the difference in degree of various symptoms. The fact that equilibration is relatively more disturbed from the posterior lesion and posture from the anterior lesion should not alter the recognition that the two functions coexist in each area. The essential similarity between a unilateral lesion of the fastigial nucleus and a unilateral lesion of the vestibular nerve or Deiters' nucleus has been pointed out by Sprague and Chambers.[52] The presence of vestibular signs following lesions in the fastigial nucleus, or in certain cortical areas projecting to this nucleus, is scarcely surprising in light of the observations of Dow,[16] who found, by the method of evoked potentials, that the eighth nerve projects to the entire nucleus, and by the anatomical work of many authors who have traced efferent fibers from the entire vermis (Jansen and Brodal [30]) and from the entire fastigial nucleus (Allen [2]; Rasmussen [42]; Thomas, Kaufman, Sprague, and Chambers [54]) to the vestibular nuclei, especially that of Deiters.

The major part of the paleocerebellum, the anterior lobe, is usually treated as a functional and an anatomical unit, and is frequently thought of as being a vermal structure. Support for this view, as cited by Fulton and Dow,[20] is that it is the chief termination of the spinocerebellar tracts, that its stimulation inhibits postural tone, and that its ablation releases vestibular reflexes and enhances postural tone. The identity of two anatomical units in the cat—a medial cortex, projecting to the fastigial (and vestibular) nuclei, and an intermediate cortex, projecting to the nuclei interpositi—was made by the important work of Jansen and Brodal.[29] These have been shown by Chambers and Sprague [14] to have distinct functional attributes. A third area in the anterior lobe, consisting of lateral cortex and dentate nuclei, has been described in the monkey (Jansen and Brodal [30]), the function of which has not yet been clearly worked out. The effects of stimulation on postural tone, mentioned above, have been shown repeatedly to be referable to the medial vermal area alone (Bremer [9]; Miller and Banting [37]; Hare, Magoun, and Ranson [25]; Chambers [13]; Moruzzi [38]; Hampson, Harrison, and Woolsey [24]; Sprague and Chambers ‡). Likewise, the classical anterior lobe syndrome is the

‡ References 52 and 53.

property of the medial cortex and fastigial nuclei only (Sprague and Chambers [52]; Chambers and Sprague [14]). Thus, the term vermis should be restricted to that cortex which projects to the fastigial (and vestibular) nuclei, while the remainder of the anterior lobe cortex in the cat projects to the nuclei interpositi and may be called paravermal or intermediate.

The proponents of the lobular theory of cerebellar localization have defined the neocerebellum on the basis of (1) its lacking spinocerebellar connections and (2) its receiving the majority of pontocerebellar fibers (Larsell,[32] Dow,[17] Carrea and Mettler [12]). On the contrary, the paleocerebellum (anterior lobe and pyramis-uvula) has been characterized by the presence of spinocerebellar fibers and the virtual absence of pontocerebellar projections. This definition has led to the inclusion of a part of the anatomical vermis (tuber and folium; simplex is often included) in the neocerebellum (Ingvar,[26] Larsell,[32] Fulton and Dow [20]), an interpretation which has formed a major obstacle to any theory of longitudinal organization. This interpretation, however, is no longer valid. The pontocerebellar fibers are now known to terminate in all parts of the cerebellar cortex, except perhaps the flocculonodular lobe (Brodal and Jansen [10]). The vermal simplex has been shown by many workers to receive spinocerebellar fibers (Brodal §), and, although these fibers do not appear to reach the tuber and folium, these areas receive analogous fibers from the head via the trigeminal nerve and nuclei (Larsell,[33] Brodal §). Moreover, the tuber or folium receives impulses from eye and ear via the tectum and tectocerebellar tracts (Snider and Stowell [51]). Stimulation of this part of the vermis controls movements of the head, body, and limbs (simplex), and of the head alone and conjugate deviation of the eyes (tuber and folium), shown by the work of Hampson, Harrison, and Woolsey [24] and that of the present paper. Stimulation of tuber and folium at somewhat higher, but still moderate, intensities has been shown to give postures of the whole body similar in all ways to those obtained by stimulation of the vermis of the anterior lobe and of the pyramis (Hare, Magoun, and Ranson [25]; Chambers and Sprague [14]). Thus, on the basis of its afferent proprioceptive, tactile, auditory, and visual projections; its efferent projection via the fastigial and vestibular nuclei, in common with the rest of the vermal cortex, and the effects following its stimulation, this vermal area is clearly a part of the total vermal zone dealing with postural mechanisms, progression, and equilibrium.

The theory of lobular organization leaves two other cortical masses unsatisfactorily defined. The paramedian lobule is classified by Larsell [32] and Dow [17] with the ansiform lobes as neocerebellar; yet its efferent projection is exclusively to the nuclei interpositi (Jansen and Brodal [30]), and its stimulation and ablation yield results similar to those obtained from the paravermal part of the anterior lobe (Ferraro and Davidoff [19]; Hare, Magoun and Ranson [25]; Chambers and Sprague [14]; present paper). The paraflocculus, which has been allied with the paleocerebellum, actually projects to the dentate nucleus (Jansen and Brodal [30]) and, like the cortex of the ansiform lobe, gives equivocal or no postural symptoms following its uncomplicated ablation (Carrea and Mettler [12]; present paper).

The present paper is based on specific lesions which were localized in the cerebellum with three concepts of organization in mind: (*a*) The lesions were placed within the anatomical confines of the corticonuclear zones, as defined by Jansen and Brodal [29]; (*b*) the lesions within these zones were restricted to either cortex and/or its efferent nucleus because of the considerable differences in function of cortex and nucleus shown by Chambers and Sprague,[14] and (*c*) certain lesions were placed so as to involve a whole lobe, comprising several zones, as defined by Larsell.[32] The work of Jansen and Brodal [29] demonstrated the nuclear components of the cortical lobes of Larsell. Our lobular lesions, therefore, attempted to destroy only the parts of the nuclei which be-

§ Brodal, A., in Jansen and Brodal,[28] Chap. 2.

longed to a particular lobe. Such restricted lesions are difficult to obtain by aspiration and are better achieved by stereotactically oriented electrodes.

MATERIALS AND METHODS

This paper is based on the study of 41 chronic cats, some of which were decerebrated terminally. The decerebrations were performed by aspirating a narrow channel through the midbrain, passing between the colliculi, dorsally, and the rostral pons, ventrally, the bed of the basilar artery and the brain rostral to the transection being left intact. The advantages of this method have been emphasized previously (Sprague and Chambers ‖). The cerebellum was exposed, great care being taken to preserve the blood supply, and warm liquid petrolatum U. S. P. was used to protect the cortical surface. Stimulation was by means of a 60-cycle sine wave current through both monopolar and bipolar electrodes. The vermal cortex, in all cases, and the paravermal cortex, in most cases, were found to be excitable. Ablations were made by aspiration.

The chronic animals were studied by stimulation through implanted concentric electrodes (Chambers [13]) and by cortical and/or nuclear destruction achieved by aspiration, thermocoagulation, and stereotactically oriented electrolytic lesions. The placement of lesions in certain areas of the cerebellar cortex was in part guided by the evoked potential studies of Snider and Stowell,[51] Adrian,[1] and Hampson.[24] These chronic animals were studied at frequent intervals throughout periods of up to four years, and in most cases until their symptoms had stabilized and compensation ceased. The only exceptions were those few animals killed after four to five days' survival for the determination of terminal connections by the method of Nauta and Gygax [40] for axon degeneration. All animals were tested before and after operation. Changes in muscle tone were ascertained by assaying resistance to passive movements of all joints with the animals lying supine or held suspended with legs hanging down; the knee jerk, supporting reactions, and tonic neck and labyrinthine reflexes were tested, as were the postural placing (tactile, proprioceptive, visual, chin) and hopping reflexes; cornea, canthus, pinna, and vibrissae were tested for response to touch; reactions of the head, limbs, and tail to nociceptive stimuli were noted; pupillary light reflexes and the response of eyes, head, and body to horizontal rotation were observed; the gait and posture both on the floor and on elevated, horizontal bars, the

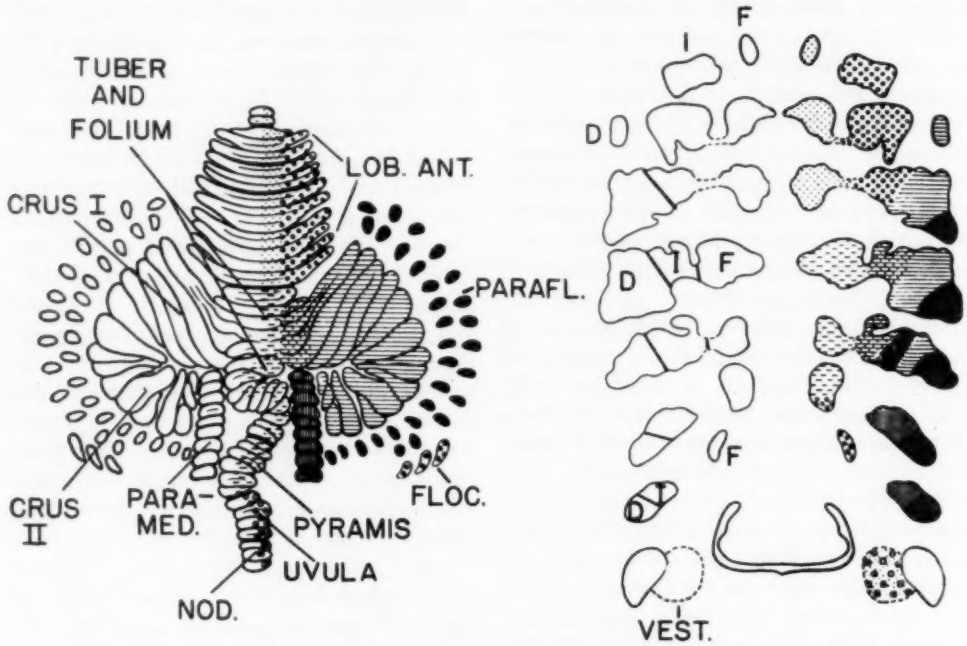

Fig. 1.—Schematic drawings, slightly modified from figures taken from the work of Jansen and Brodal (J. Comp. Neurol. **73**:267-321, 1940; published by the Wistar Institute of Anatomy and Biology, Philadelphia), showing the longitudinal organization between cortex nuclei of the feline cerebellum: *D* (dentate nucleus); *I* (nucleus interpositus); *F* (nucleus fastigius).

‖ References 52 and 53.

capacity for righting in air, jumping up or down and gauging distances were studied, as was volitional activity in playing, fighting, and feeding; the ability to maintain balance was measured by the adjustment of body posture to sudden or steady push in various directions; observations were made, where possible, on changes of motivation and behavior.

Previous work (Sprague and Chambers ¶; Chambers and Sprague [14]) has shown the importance of determining the specificity of the lesions in the zones and lobes, as well as the relative involvement of the cortex and nuclei of those zones. This was determined by terminal decerebration and stimulation of the areas surrounding the lesions and by histological sections stained by the Marchi, Weil, or Nissl method. Thus, statements of the extent of the lesions in the following description are based on a detailed physiological and anatomical mapping (Fig. 1).

¶ References 52 and 53.

RESULTS

I. Ablation of Entire Anterior and Posterior Lobes

A. Almost total destruction of the anterior lobe bilaterally, back to the primary fissure and including the rostral one-third of both fastigial nuclei and the rostral poles of the nuclei interpositi, especially on the left side (right side of Figure; one animal, 80 days' survival, Fig. 2), showed the following symptoms on the second and third postoperative days: marked spasms of opisthotonos; spasticity of entire body; wild, forced movements; plaintive crying; rapid vertical clonus of eyes with head dorsiflexed; panting, sweating of paws, and dilatation of pupils after handling; visual and chin placing wild and grossly dysmetric in forelegs; tactile and proprioceptive placing absent in hindlegs. Clear-cut

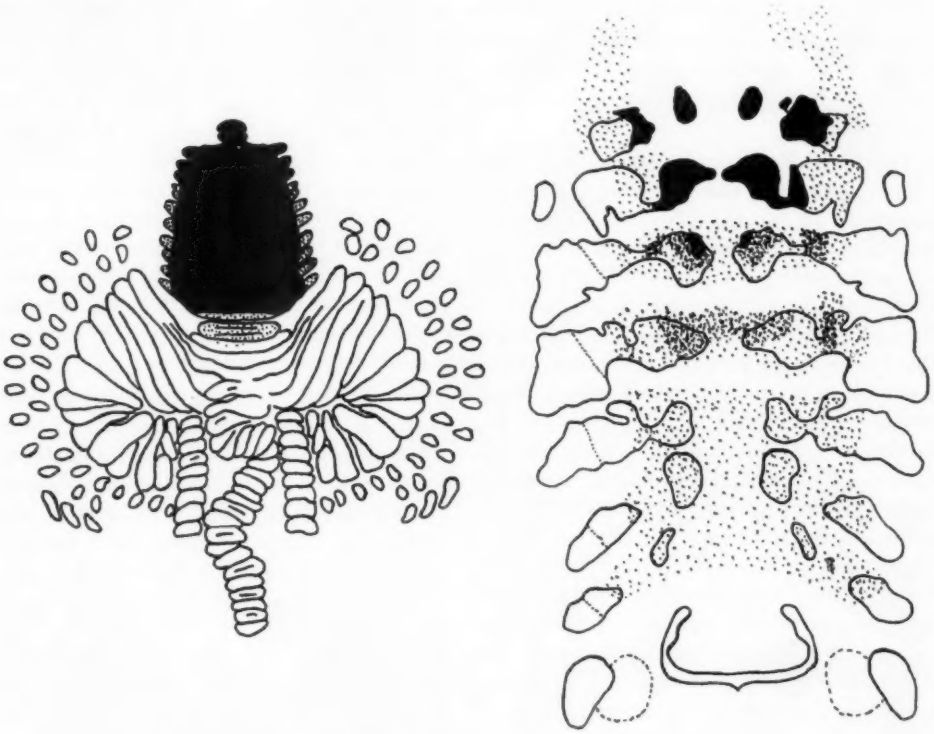

Fig. 2.—Schematic drawings of cerebellar cortex and nuclei, showing lesions (black) and secondary gliosis (dots) in the anterior lobe.

asymmetry was present in that the animal preferred to lie on the left side; the left limbs showed greater extension and the right legs greater flexion; visual and chin-placing responses were brisker in the right forelegs, as were the movements to dislodge the observer's hand; tactile placing and hopping were absent in the left foreleg (present, but slow and hypermetric in the right); supporting reaction was absent in the right foreleg and minimal in the right hindleg and was stronger in the left legs. This animal ate voluntarily on these days and showed hypotonic bladder and partial righting in the forequarters. No resting nystagmus or rolling was present.

The opisthotonos had disappeared by the 17th postoperative day (no observations between the 3d and the 17th day); the spasticity was reduced, and spasms of hypertonus alternated with quiet periods. The head and forequarters were righted to a sphinx position, with swaying of the head, and, although standing was not possible, the animal could slowly drag his body by the forelegs. Poor proprioceptive placing and hopping had returned to the hindlegs; otherwise, placing reactions had not changed but remained asymmetric. Supporting reactions were now present in the right legs, but, like the hypertonia, were stronger in the left legs. Constant purring and kneading accompanied high pain threshold. Excessive postrotatory nystagmus was present. Hypotonia of the bladder and constipation were marked. Other symptoms were unchanged except for greater ataxic tremor of the head and body.

No improvement was found on the 28th postoperative day. The next examination, on the 76th to the 80th day, revealed righting in both fore- and hindquarters, with lateral swaying and tendency to fall in the hindquarters. Walking was hesitant, in a low crouch with marked ataxia, and was accomplished with great difficulty, and then only for a few steps. Tactile placing to touch of the lateral surfaces of the forefeet and ankles had returned to both forelegs (incomplete in left foreleg) and to plantar touch in the right hindleg (tactile placing was absent in the left hindleg). Visual placing was equally wild in the two forelegs. Proprioceptive placing and hopping had improved, although still slow and hypermetric in all legs, and was better on the right side. Supporting reactions were greater on the left side. Head pecking while eating, bladder hypotonia, constipation, and high threshold to painful stimuli persisted.

B. The posterior lobe cortex, caudal to the simplex lobule, plus the flocculonodular lobe and the caudal one-third to one-half of the fastigial nuclei and nuclei interpositi and the entire dentate nuclei (two animals, survival 12 to 149 days; Figs. 3 and 4) were ablated. The syndrome of the first and second postoperative days was as follows: marked opisthotonos with great increase in extensor tone; righting to sphinx position but no standing or walking; stiff, hypermetric stepping in forelegs when held by hindquarters; reductions in placing and hopping reflexes; pupils enlarged and light reflexes sluggish, and no rolling or nystagmus.

Standing and walking, when begun, were slowly and reluctantly executed and were accompanied by marked swaying backward and forward, head bobbing, low crouch (somewhat higher in forequarters), and broad base. As walking improved, the general instability, tremor, and ataxia became more marked, and frequent falling followed any sudden movement. This phase of recovery was one of hyperactivity, in contrast to the condition in the first few days, and was accompanied by a lack of discretion, so that falls and head injuries were not uncommon. The animals persistently attempted to descend from a high table when the righting reflexes were only partly recovered. Eventually walking and jumping were improved, although the animals always showed a stiff gait, broad base and crouch, swaying, and goose-stepping in the forelegs. However, the postural and equilibratory requirements of walking on elevated, horizontal bars remained far beyond the capacities of the animals with these lesions.

Certain important differences were correlated with the extent of the lesions, par-

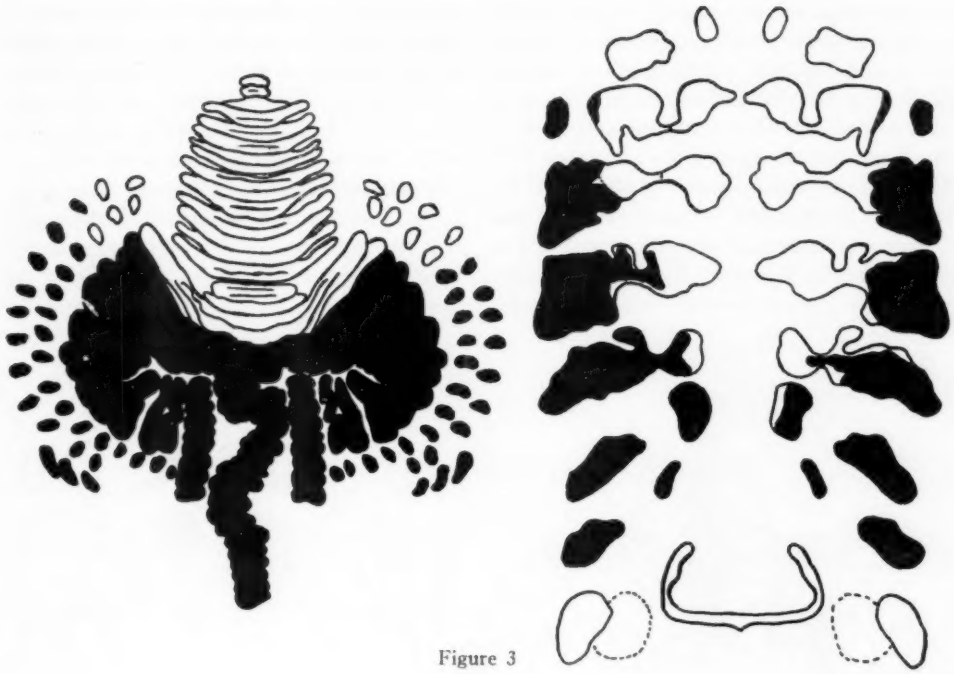

Figure 3

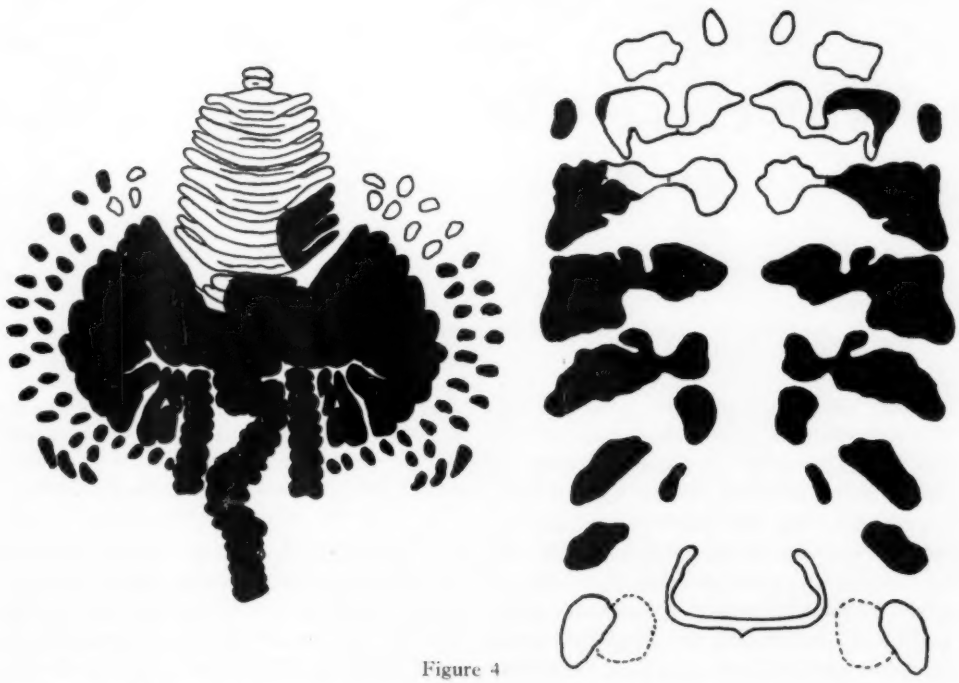

Figure 4

Figs. 3 and 4.—Schematic drawings of cerebellar cortex and nuclei, showing lesions in the posterior lobes.

ticularly with the involvement of the medial and intermediate nuclei. One animal (Fig. 3), which had the lesion restricted to the caudal parts of the fastigial nuclei and nuclei interpositi, showed less severe symptoms of opisthotonos and hypertonus and head bobbing, less involvement and earlier improvement of placing and hopping reflexes, and earlier appearance of standing and walking (fourth day). The second animal (Fig. 4), with more rostral destruction of the nuclei, showed less complete recovery at the 39th day than the first animal showed at the 12th day. In addition, all placing and hopping reflexes were abolished for the first week in the animal with the larger lesion, and remained permanently depressed and hypermetric in all legs except the right foreleg, in which tactile placing was permanently abolished and other placing and hopping reflexes were more severely affected. That the deficits in the right foreleg were due to the rostral extension of the lesion into the right nucleus interpositus is confirmed by the presence of certain other symptoms known to be caused by selective lesion of the nucleus interpositus (see Section III): instability of wrist, misplacement of leg with skating movements, and standing on the dorsum of the foot.

These animals showed that, despite the initial severity of the symptoms, the major part of improvement through compensation was accomplished between the ends of the first and second weeks. A relative stability was present thereafter, with only slow and insignificant recovery in the following period.

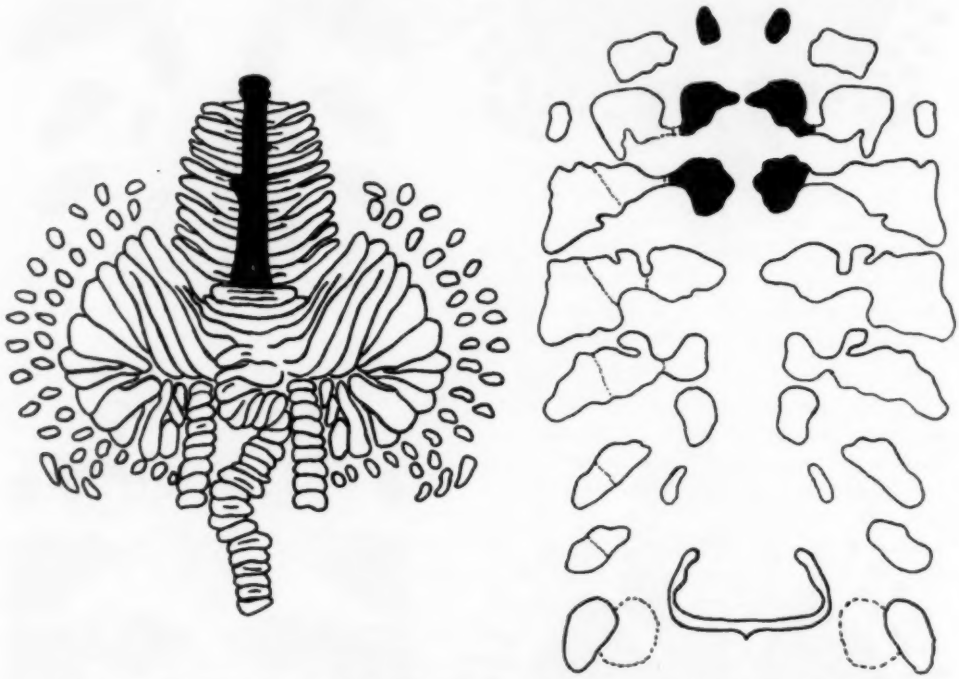

Fig. 5.—Schematic drawings of cerebellar cortex and nuclei, showing lesion in the vermal zone of the anterior lobe.

II. Lesions Limited to the Vermal Zone (Cortex and Fastigial Nuclei)

A. Ablation of the entire vermal cortex of the anterior lobe, extending back to the primary fissure and including the rostral one-half of the fastigial nuclei (one animal, 12 days' survival; Figs. 5 and 26) resulted in the following syndrome on the first postoperative day: marked increase in tone,

chiefly extensor, and strong and almost constant opisthotonos; no rolling or nystagmus; ability to maintain sitting position with forelegs stiffly extended, hindlegs extending forward, back concave, and head dorsiflexed; bursts of head tremor at rest; with animal suspended in air, legs stiffly extended, with toes fanned and claws out; all placing responses hyperactive, hopping hypermetric; no walking or stepping in forequarters when held by hindlegs and pelvis; when held by forequarters, hindlegs widely spread and tail dorsiflexed; bladder hypotonic, 60 cc. urine expressed manually.

Stepping in fore- and hindlegs was possible when the body was supported on the second postoperative day; marked disturbance of balance was obvious, as was tendency to climb with forelegs and accompanying retropulsion; 20 cc. of urine was expressed manually.

The animal could stand alone on the fifth and sixth postoperative days and take a few steps with a broad base, high in forequarters, low in hindquarters, tail dorsiflexed, swaying of entire body, tremor of head and tail; walking was very slow, high on the toes, with frequent falling backward and to either side; the bladder emptied voluntarily.

There was a subsequent slight decrease of extension of limbs and of opisthotonos, and an increase in general activity accompanied by more frequent falling, up to the 12th day, when the experiment was terminated.

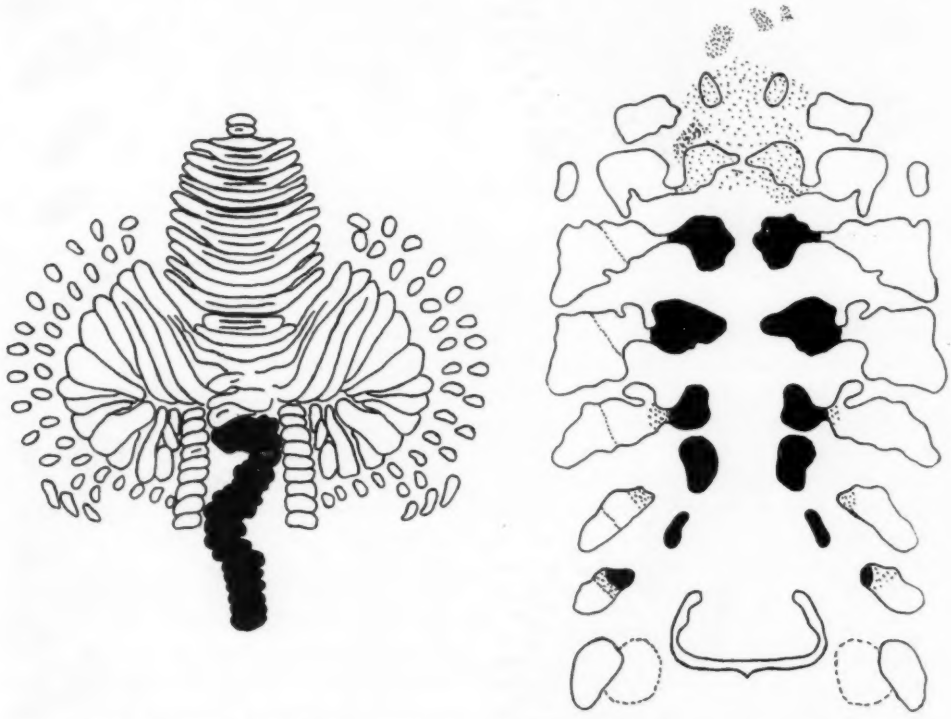

Fig. 6.—Schematic drawings of cerebellar cortex and nuclei, showing lesion (black) and gliosis (dots) in the vermal zone of the posterior lobe, with slight encroachment of the medial-caudal tips of the interpositus nuclei.

B. Ablation of the entire vermal cortex of the posterior lobe, except the simplex and folium, and including the nodulus and the caudal three-fourths of the fastigial nuclei (one animal, 42 days' survival; Fig. 6), resulted in a syndrome which was strikingly similar to that following the anterior vermal lesion. In both, the tone, equilibrium, and

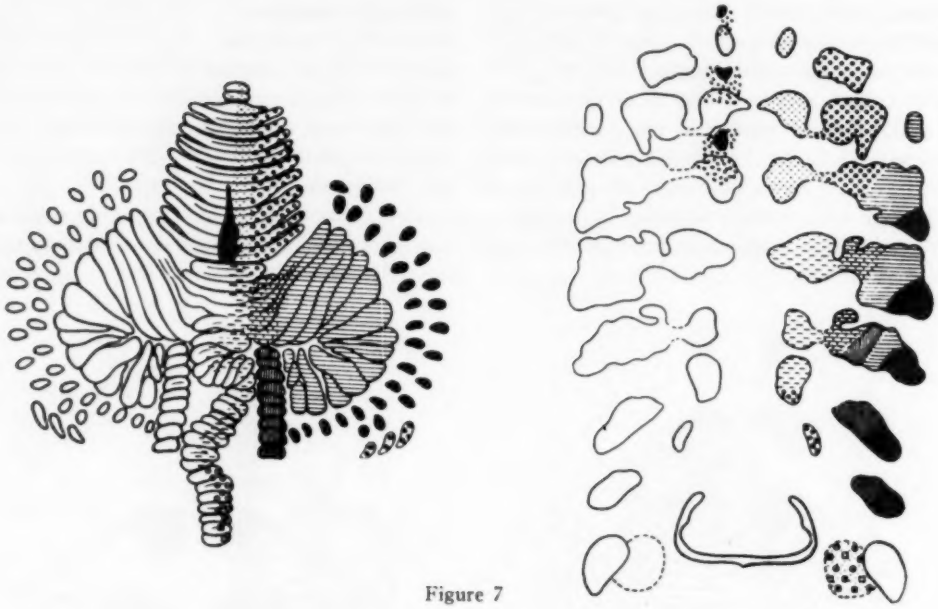

Figure 7

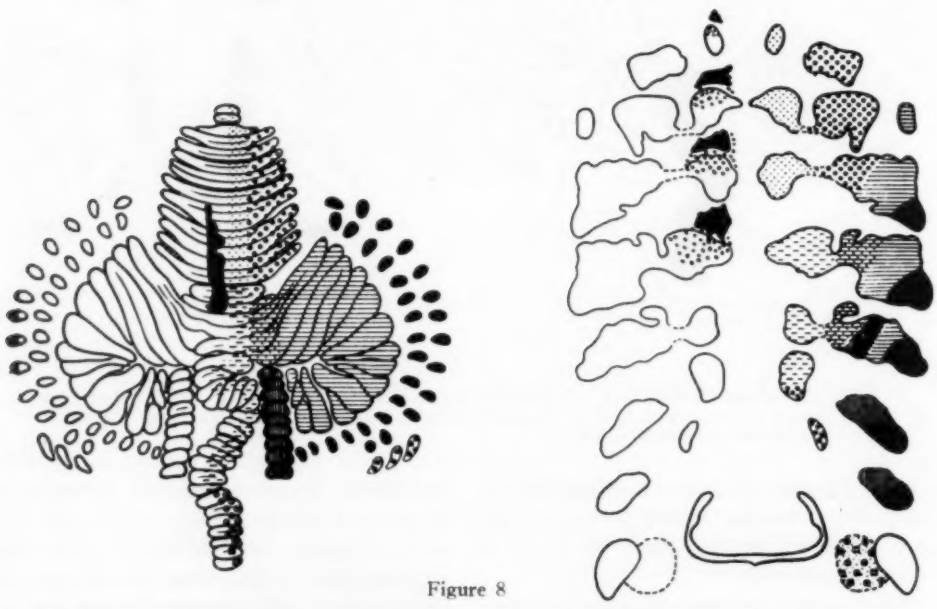

Figure 8

Figs. 7, 8, and 9.—Schematic drawings of cerebellar cortex and nuclei, showing lesions (black) and gliosis (dots) of the anterior lobe and lobulus simplex (left side of Figure). The right side of these figures, and of many subsequent figures, show the zonal, corticonuclear relationships, according to Jansen and Brodal (J. Comp. Neurol. **73**:267-321, 1940; published by Wistar Institute of Anatomy and Biology, Philadelphia).

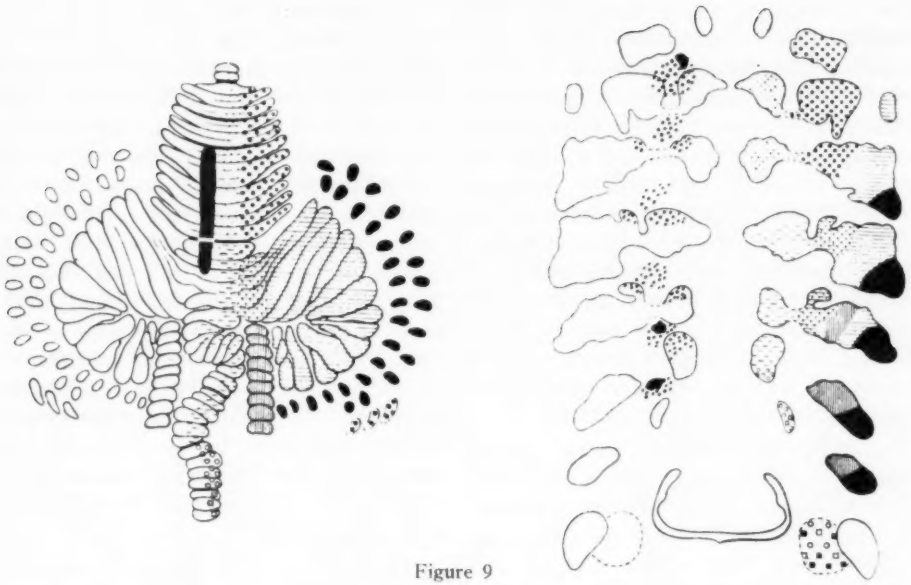

Figure 9

progression of the whole body showed great impairment. Also characteristic of the lesions was the plaintive crying which accompanied passive or active change of the position of the body. The spasticity and opisthotonos, although present in the posterior vermal lesion, were less marked than in the anterior vermal lesion; the body was held closer to the ground, and movement consisted of rapid backing ("crawfishing"). At no time was there falling or a tendency to climb. Standing was accomplished by the fifth day, accompanied by a broad base and a marked swaying of the body forward and backward. Walking, begun on the seventh day, was not high on the toes, but the forelegs showed both overstepping and high stepping. Between the 7th and the 42d day the symptoms remained relatively stable, but more activity, walking, and falling were present.

C. Ablation of the vermal cortex in the anterior lobe has been described previously in two animals, of 42 and 14 days' survival (Chambers and Sprague [14]). These lesions were unilateral and involved the caudal five folia of the culmen in one animal (Fig. 7) and the caudal five and one-half folia of the culmen plus the two folia of the simplex in the other animal (Fig. 8). Initially, the symptoms involved the whole body—extension of ipsilateral legs, flexion of contralateral legs, falling to opposite side, head and body concave to opposite side; but the deficits in the hindlegs disappeared rapidly (two to three days). The first animal, with the smaller and shallower lesion, entirely rostral to the primary fissure, was asymptomatic by the 10th day; the second animal showed marked symptoms at the end of 14 days and had a greater involvement of the head.

A third animal (seven days' survival), with a unilateral, shallow cortical lesion restricted to the vermis of the anterior lobe (culmen and caudal folia of the centralis), showed symptoms similar to, although milder than, those of the first animal, except for greater involvement of the hindquarters. After three days a second lesion was added to the simplex of the same side, which caused a marked turning of the head and concavity of the body to the opposite side (Fig. 9). On the first postoperative day following the lesion in the simplex, this animal showed a reversal of the distribution of tone in the legs (especially the forelegs), instability of the left wrist and a high step of this foreleg, misplacement of the left foreleg when walking on elevated bars, and a great increase

in sensitivity to its tactile placing. The tone reverted to the original state, and the other symptoms were reduced on the second day; by the seventh postoperative day the original distribution of tone (ipsilateral extension, contralateral flexion) had become further increased in the forelegs, and the aberrant symptoms had disappeared. The transient shift of tonus and the appearance of hyperflexion, instability, and hyperexcitability of the ipsilateral foreleg were explained by the accidental extension of the simplex lesion into the caudal portion of the paravermal zone in the anterior lobe (see description of paravermal lesions, and Figure 8).

In a fourth animal, a small vermal cortical lesion was placed unilaterally in the third and fourth folia rostral to the primary fissure. The animal was killed four days later for silver staining. The animal righted and walked (without defect) immediately after recovery from the anesthesia. The only deficit found during the survival period was a small increase in extensor tone in the ipsilateral foreleg. No abnormality in placing, hopping, deep reflexes, or supporting reaction was present.

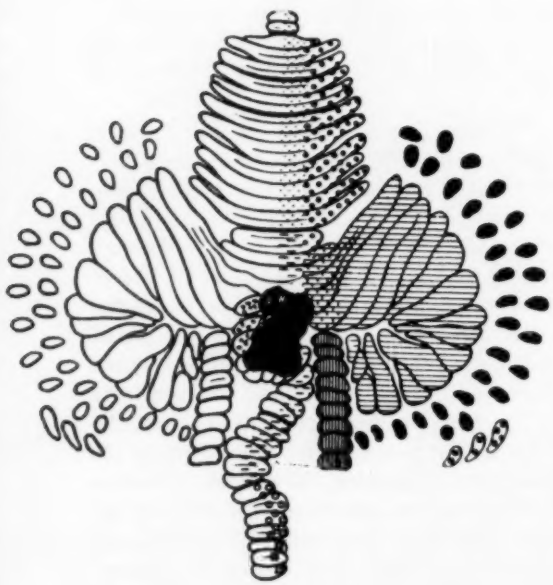

Fig. 10.—Schematic drawing of cerebellar cortex, showing lesion of the folium and tuber.

D. Ablation of the vermal cortex of the so-called middle lobe was made bilaterally from the 3d to the 11th folium behind the primary fissure, and thus did not involve the simplex or the pyramis (one animal, 40 days' survival; Fig. 10). Between the first and fourth postoperative day, moderate hypokinesia was present, with only slight response to visual and auditory cues. Rather marked difficulties in gauging distances properly when jumping were found. Other changes were slight and consisted of stiffness in the neck, increase in extensor tone in all legs (more in the forelegs), goose-stepping in the forelegs, resting head tremor, reduced movement of the eyes and head, increase in postrotatory nystagmus, and hypermetria of otherwise normal placing and hopping reflexes.

All symptoms were present but improved by the fifth day, except for continued poor attention and response to light and, especially, to sound. The response to visual cues was back to preoperative alertness by the sixth day, although there was a marked tendency for his visual attention to become fixed for considerable periods. The seventh day found all reflexes and motor activity normal except for the retention of a slight goose step in the forelegs, an unusual bounding instead of the customary running gait, and hesitation in jumping even small distances, with repeated reaching out of the forelegs toward the desired goal (the jump was smoothly and normally executed). All symptoms remained to the 40th day, and, although there was some improvement in the response to various sounds, the defect was still striking.

All of the defects found in this animal after the lesion were in marked contrast to his preoperative state of extreme alertness, curiosity, agility, and auditory and visual responsiveness.

E. Destruction of one entire fastigial nucleus has been described previously in two animals, of 7 and 22 days' survival (Sprague and Chambers #). The deficits involving the

References 52 and 53.

posture, gait, and equilibrium of the entire body were grave. The ipsilateral legs were flexed; the contralateral, extended; the head turned to the side of the lesion, and the body was concave to this side. Righting and walking were more impaired and falling was severer and more frequent than following cortical lesions of this zone. Placing reflexes were hyperactive and hopping hypermetric (see also Figure 3*C* of Thomas and associates [54]).

tigial nucleus (one animal, survival four days; Fig. 11), the symptoms were confined chiefly to the hindlegs: The ipsilateral leg was flexed and adducted and showed a decreased supporting reaction; the hindlegs took small, stiff steps, accompanied by swaying. That the fore end of the animal was also involved was suggested by circling to the side of the lesion and pivoting on the ipsilateral hindleg. The animal was alert and active and walked and ate voluntarily.

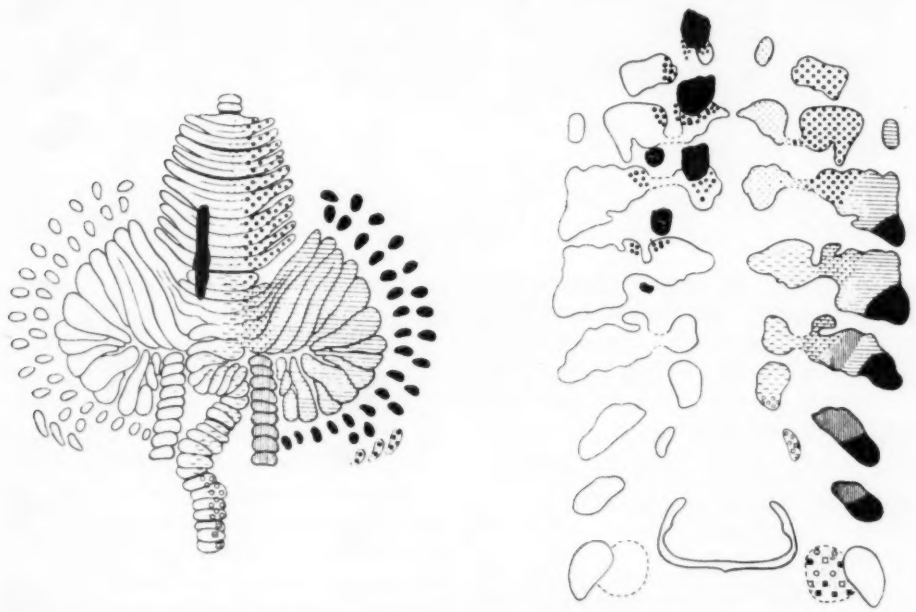

Fig. 11.—Schematic drawings of cerebellar cortex and nuclei, showing lesions (black) and gliosis (dots) in the rostral pole of the nucleus fastigius (left side of Figure).

Selective unilateral destruction confined to the rostral one-half of the fastigial nucleus (one animal, survival four days; Fig. 1 of Thomas and associates [54]) showed symptoms which were more pronounced in the hindlegs, although the whole body was involved. Righting and walking were accomplished with difficulty, with falling in the hindquarters toward the side of lesion. Supporting reactions and resting extensor tone were greater in the contralateral legs, while the ipsilateral legs were flexed. The animal did not eat voluntarily and was reluctant to move. When the lesion was somewhat more limited to the most rostral pole of one fas-

In neither animal was there any pupillary change.

In another experiment, the nuclear lesion was limited to the middle one-third of the fastigial nucleus (one animal, four days' survival; Fig. 3*A* of Thomas and associates [54]) and showed deficits limited to the forelegs: increased supporting reaction and resting extensor tone in the contralateral leg; increased flexion in the ipsilateral leg.

Destruction of the caudal one-third of the fastigial nucleus on one side (one animal, survival four days; Fig. 3*B* of Thomas and associates [54]) resulted in lethargy, reluctant walking in a low crouch and with a broad

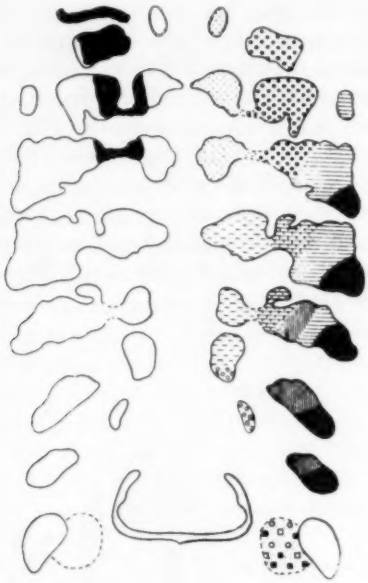

Figure 12

base, a tendency to flex the limbs and to grasp with claws, and resistance to being placed in a supine position. The distribution of tone was similar to that in the other partial nuclear lesions, and the head was turned to the side of lesion.

III. Lesions Limited to Paravermal or Intermediate Zone (Cortex and Nuclei Interpositi)

A. Unilateral ablation of the entire nucleus interpositus has been described previously in four animals, of 4, 17, 340, and 822 days' survival (Chambers and Sprague [14]). The postural symptoms were limited to the legs of the same side of the body and consisted of mild, but clean-cut, increase of extensor tone and the supporting reflex; permanent loss of tactile placing and temporary depression of proprioceptive placing and hopping, with permanent hypermetria of these reflexes; goose-stepping, stiffness and instability in walking, and severe misplacement of the ipsilateral legs on elevated bars, and diminution and fatigability of flexor movements. The pupil and palpebral fissure of the ipsilateral eye were enlarged, and the nictitating membrane was partly extended on the contralateral side.

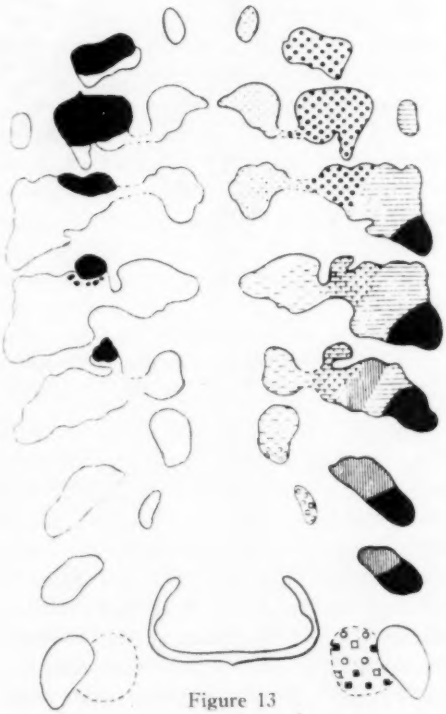

Figure 13

Figs. 12, 13, and 14.—Schematic drawings of cerebellar cortex and nuclei, showing lesions (black) and gliosis (dots) in the rostral and in the middle and caudal parts of the nucleus interpositus (left side of Figure).

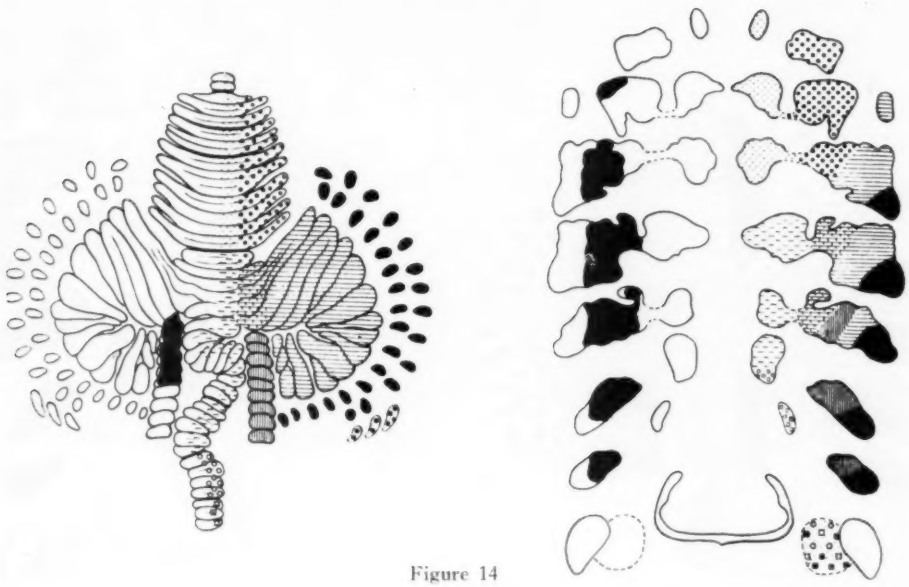

Figure 14

B. Lesion of the rostral tip of one nucleus interpositus of one animal surviving 166 days (Fig. 12) showed symptoms in both legs of the ipsilateral side: goose step; increased extensor tone, loss of tactile placing, and presence of hypermetric hopping in the ipsilateral foreleg. Contact placing returned after the first week; hopping and tone were normal by the 12th postoperative day, and the goose step had disappeared by the 40th day. The ipsilateral hindleg, however, showed these symptoms throughout the survival period; in addition, it showed circumduction and abduction in walking, and frequently assumed bizarre positions at rest. No change in pupils, palpebral fissures, or nictitating membranes was found.

A lesion which was again limited to the rostral part of one nucleus interpositus, but which was larger than the preceding lesion (Fig. 13), was placed in one animal, surviving four days. The symptoms were essentially the same as those following total nuclear destruction (Section III A), except for less severe impairment of proprioceptive placing and lack of any change in pupils or eyes.

Unilateral lesion of the middle and caudal parts of the nucleus interpositus (Fig. 14) in one animal, surviving 27 days, resulted in goose step in the ipsilateral foreleg and high step and limping in the ipsilateral hindleg for the duration of the experiment. Contact placing was absent in the ipsilateral foreleg for six days, and impairment in hopping in both ipsilateral legs was present for nine days. The eyes were not observed.

C. Ablation of the entire paravermal cortex of the anterior lobe was accomplished in one animal,* with a subsequent survival of 58 days (Figs. 15 and 27*A*). In most cases the symptoms were the reciprocal of those following lesions in the nucleus interpositus, and were again limited to the ipsilateral limbs. The animal walked without disturbance of balance, but with marked hyperflexion of both ipsilateral legs and instability at wrist and ankle. This did not take the form of the stiff goose step characteristic of the nuclear lesion but had two phases, both exaggerated: The first was a hyperflexion at all joints; the leg was held momentarily in this position and then suddenly brought forward and down in the second phase, resulting in a limp step. The deficit is clearly in the synergy and reciprocal innervation of the musculature of limbs and girdles, although the stepping sequence be-

* Animal referred to in III E.

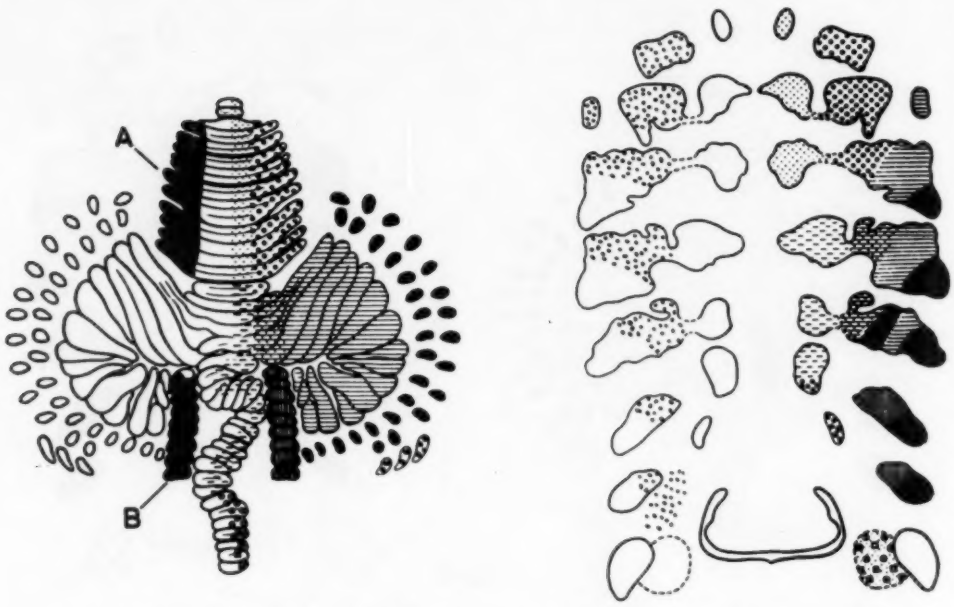

Fig. 15.—Schematic drawings of cerebellar cortex and nuclei, showing lesion (black) and gliosis (dots) in the paravermal zone of *A*, the anterior lobe, and *B*, the paramedian lobule (left side of Figure).

tween fore- and hindlimbs was not affected. At rest, the foreleg was frequently held off the ground, flexed, and the hindleg was often held aloft when walking had stopped at this phase of the stepping sequence or when the animal stretched his hindquarters. The resting tone was shifted to flexion in the ipsilateral limbs; and when the animal was suddenly lifted from the ground or pushed to the opposite side, these limbs immediately flexed. Tactile placing and hopping were dysmetric in both ipsilateral legs,

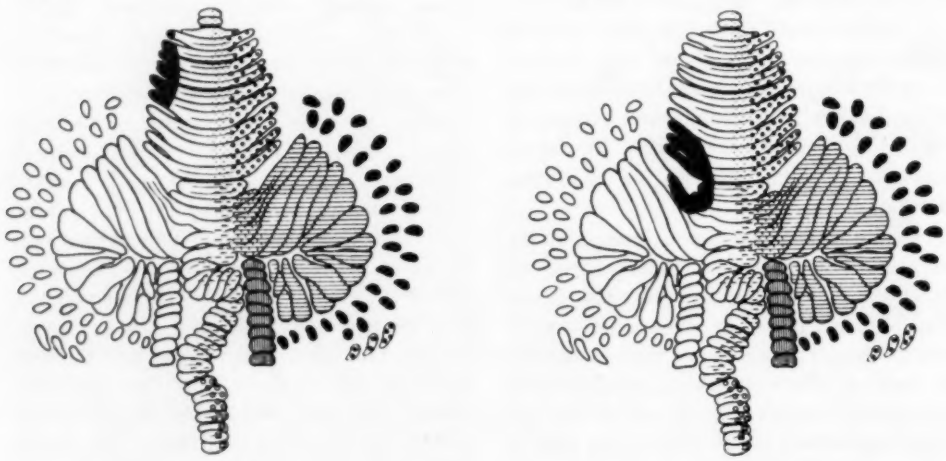

Fig. 16.—Schematic drawings of cerebellar cortex showing lesions (black) in the paravermal zone of the anterior lobe (*A*), and (*B*) including the simplex (left side of Figure).

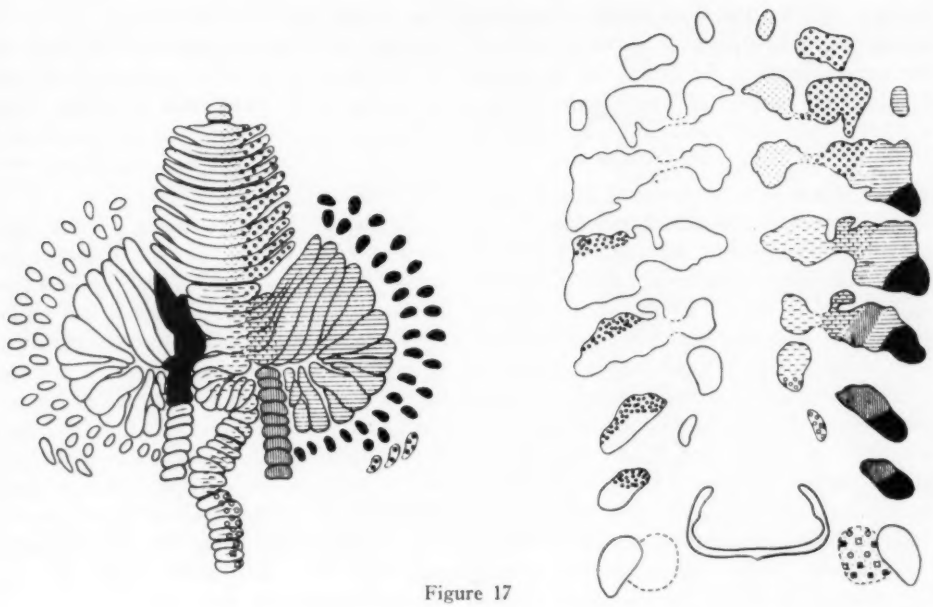

Figure 17

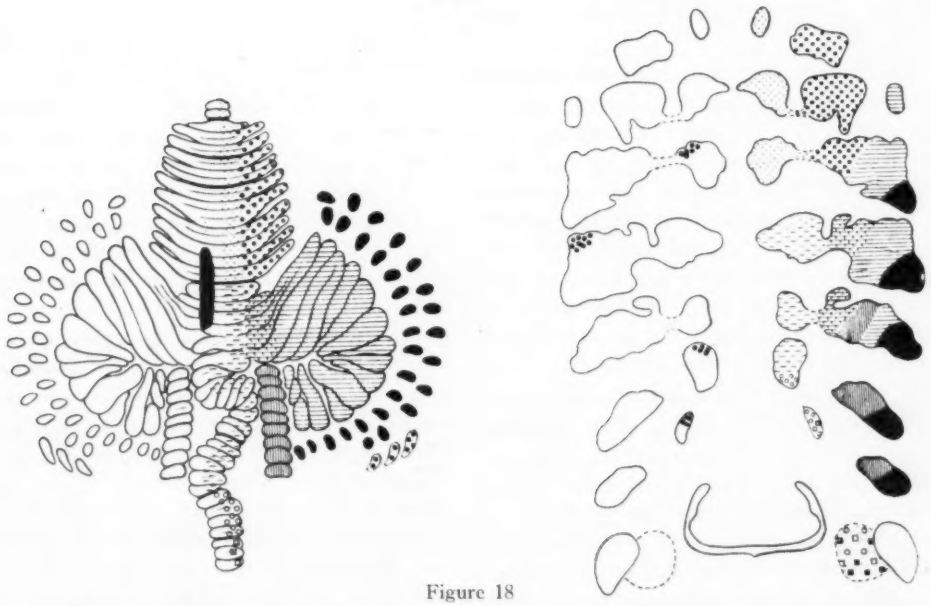

Figure 18

Figs. 17 and 18.—Schematic drawings of cerebellar cortex and nuclei, showing lesion (black) and gliosis (dots) in the paravermal zone of the posterior lobe (Fig. 17) and of the anterior and posterior lobes (Fig. 18) (left side of Figure).

and these legs were misplaced badly, causing falling when the animal attempted to walk on elevated bars. Marked piloerection along the dorsum of the back, especially at the base of the tail, was present. The symptoms persisted, somewhat less marked, through the survival period. The ipsilateral pupil was enlarged for the first five days.

Unilateral ablation of the rostral paravermal cortex in two animals, surviving

3 days (5th to 10th folia ahead of primary fissure) and 159 days (Fig. 16*A*) showed the same symptoms, limited to the ipsilateral hindleg. The animal of longer survival had a more superficial lesion and was asymptomatic by the 89th postoperative day.

The effects of lesions placed in the paravermal cortex of the caudal four folia of the anterior lobe, and into the posterior lobe as far as the rostral paramedian lobule, surviving 9, 30, 104, and 159 † days (Fig. 19*A*) have been described previously (Chambers and Sprague [14]). These animals showed symptoms similar to those described above, but limited to the ipsilateral foreleg. An additional animal ‡ with a unilateral lesion in the paravermal cortex of the caudal anterior lobe (three folia ahead of the primary fissure) and of the simplex (two folia behind the primary fissure) again showed similar symptoms localized to the ipsilateral foreleg during a survival period of seven days (Fig. 16*B*).

D. Two animals with unilateral paravermal lesions involving the simplex, folium, and tuber (middle lobe of Ingvar) with slight involvement of Crus I, together with the rostral three folia of the paramedian lobule in one animal (four days' survival; Fig. 17), and the caudal three folia of the culmen in another (five days' survival; Fig. 18), showed mild symptoms limited to the foreleg, and dilatation of the ipsilateral pupil for the first three to four days.

E. Total removal of one paramedian lobule in two animals (76 and 94 days' survival; Figs. 15*B* and 19*B*) resulted in symptoms similar to those following ablation of the entire paravermal cortex of the anterior lobe, but were much milder. The first animal was asymptomatic by the 14th day, and the second animal had lost all symptoms by the 10th day, except hyperactive tactile placing and hopping in the ipsilateral foreleg, which lasted through the survival period. After 18 days the first animal had a subsequent lesion which destroyed the entire paravermal cortex of the anterior lobe (Fig. 15*A*). The animal survived an additional 58 days and is described above. The second animal, after a period of 97 days, had a smaller lesion placed in the paravermal cortex, caudal anterior lobe, and simplex and was killed seven days later (III C, Fig. 19*A*).

Partial unilateral ablation of the paramedian lobule was accomplished in two animals (Fig. 20*A* and *B*), which showed transient symptoms. When the lesion was limited to the rostral three folia (76 days' survival), a slight high step was present in the ipsilateral foreleg for two days. Destruction of the caudal four and one-half folia (12 days' survival) resulted in dilatation of the contralateral pupil for one day, loss of tactile placing in the ipsilateral hindleg for one day and in the ipsilateral foreleg for four days, and high step and weakness in the ipsilateral hindleg for four days.

IV. Lesions Limited to the Lateral Zone (Cortex and Dentate Nuclei)

A. Near-total destruction of one dentate nucleus and most of the white matter of Crura I and II (one animal, 13 days' survival; Fig. 21) resulted in symptoms limited to the ipsilateral limbs. Loss of tactile placing; impairment of visual, vestibular, and proprioceptive placing; reduction of hopping, and general poverty of individual limb movements were observed throughout the survival period. There was no detectable alteration in postural tone and supporting reflex and knee jerks. This animal walked without impairment on the floor and jumped from a height of 3 ft. without defect. However, when he was walking on raised horizontal bars, a slight misplacement of the ipsilateral feet was seen, but there was no oscillating-limb, searching movements or tendency to fall, such as were seen in the interpositus lesions. Only a slight change in these symptoms occurred during the survival period. The hopping reflexes and the postural placing reflexes (vestibular, visual, and proprioceptive) became brisker by the eighth day, although they remained hypermetric and of high threshold.

† Animal referred to in III E, Fig. 19*A*.

‡ Animal in Figure 16*B*.

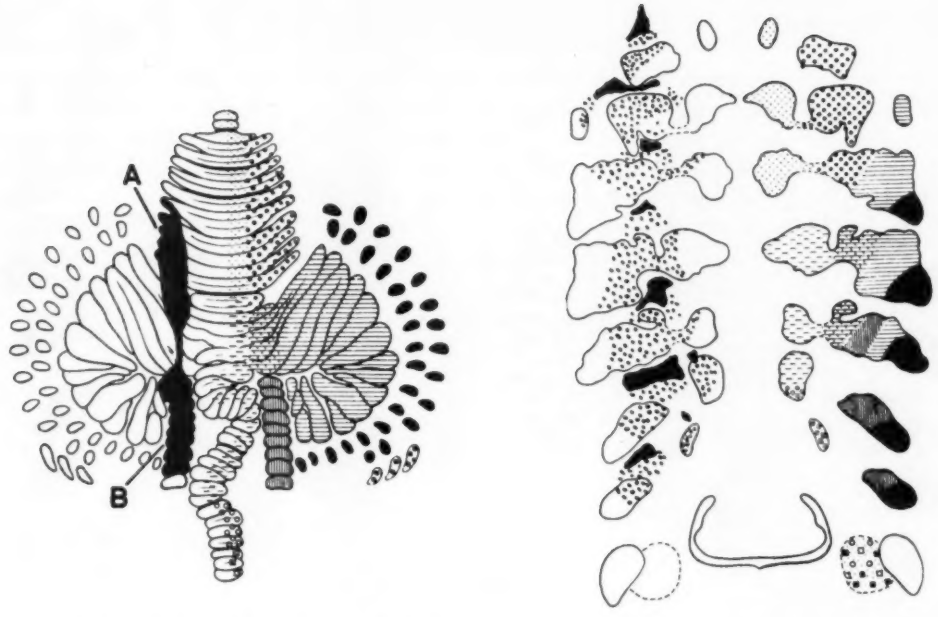

Fig. 19. Schematic drawings of cerebellar cortex and nuclei, showing lesion (black) and gliosis (dots) in the paravermal zone of (*A*) anterior and posterior lobes and (*B*) paramedian lobule only (left side of Figure).

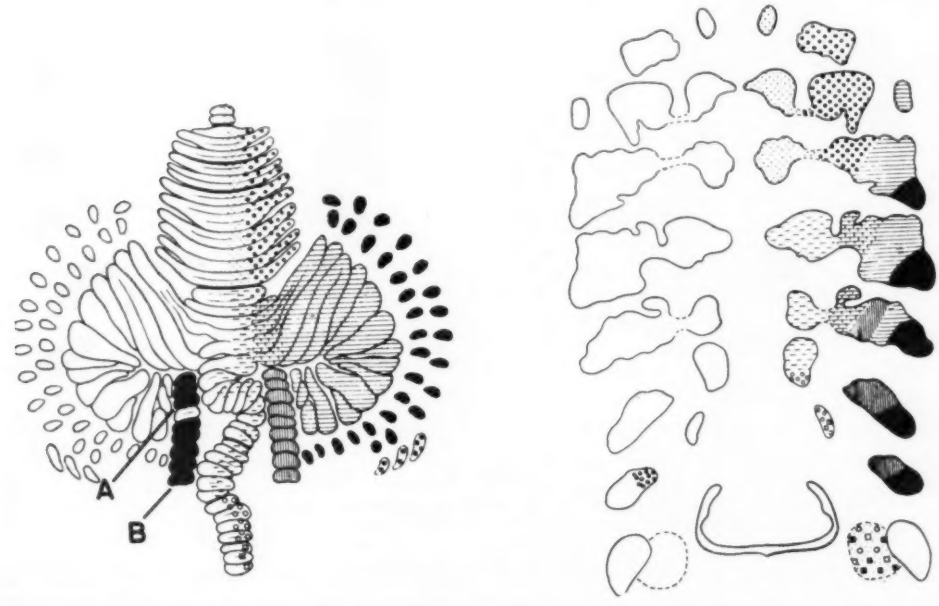

Fig. 20.—Schematic drawings of cerebellar cortex and nuclei, showing lesion (black) and gliosis (dots) in the rostral (*A*) and caudal (*B*) parts of the paramedian lobule (left side of Figure).

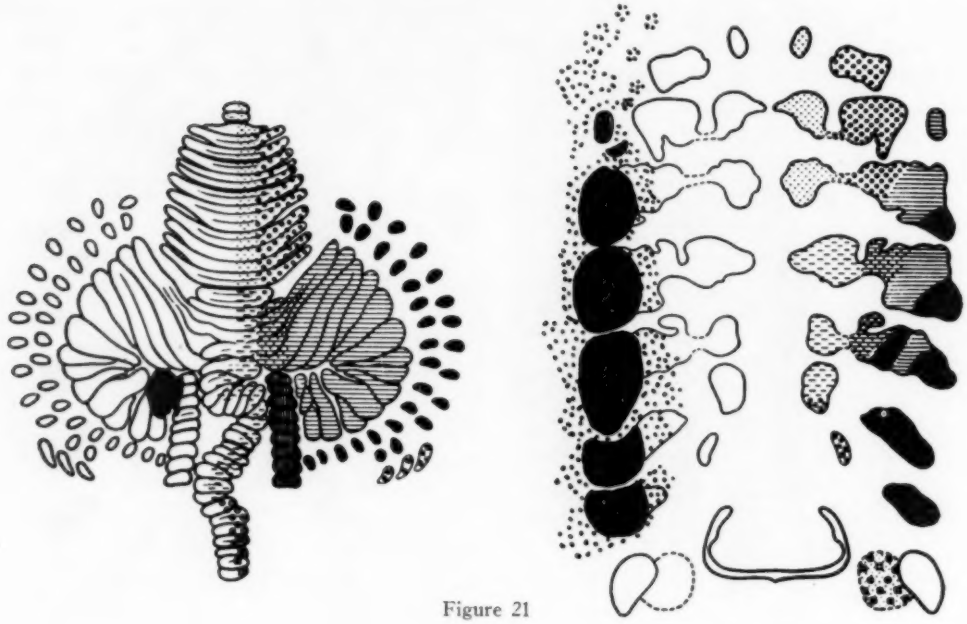

Figure 21

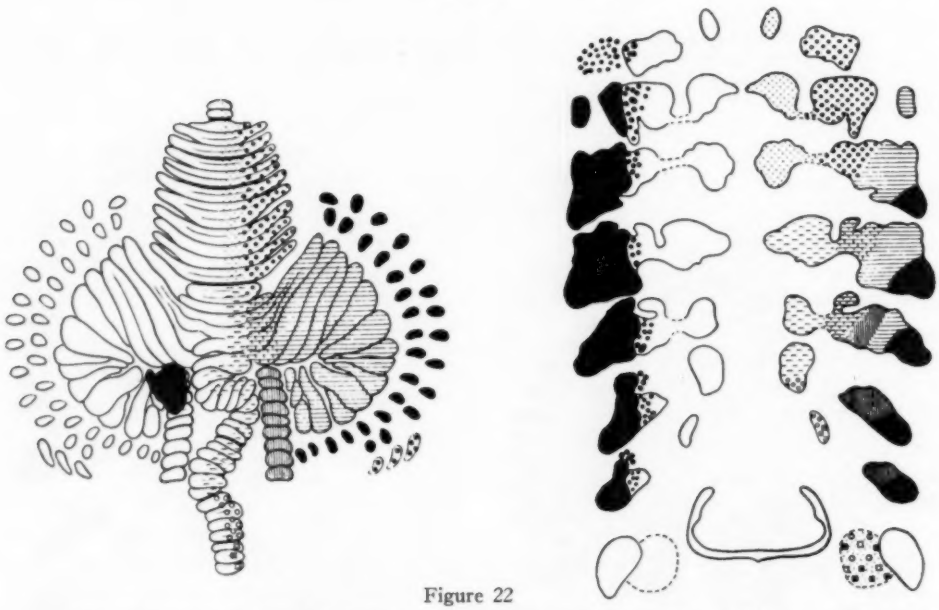

Figure 22

Figs. 21 and 22.—Schematic drawings of cerebellar cortex and nuclei, showing lesion (black) and gliosis (dots) in the dentate nucleus (left side of Figure).

The most striking symptoms—the total loss of tactile placing and the poverty of certain movements—were especially interesting because of the lack of changes in tone and deep reflexes and the absence of any abnormality of limb position or of any deficit in walking on the floor. The poverty of movement was as follows:

(*a*) When the cat was held in the air for testing placing reactions, the ipsilateral limbs

were immobile, did not show searching movements, and were not generally used to attempt to dislodge the observer's hand.

(*b*) When the animal was held in the air and suddenly lowered, to test vestibular placing, the ipsilateral limbs showed brisk toe fanning but did not follow this with extension of the leg and dorsiflexion of the wrist and ankle, seen on the opposite side.

(*c*) When the animal was held supine for testing of tone and supporting reflexes, the ipsilateral limbs showed lack of variability in tone. They did not withdraw when passively extended, nor did they respond (flexion avoidance) to touch or pinprick. When the prick was strong, the animal's protest consisted of crying and striking with the contralateral legs, an observation which indicates that some motor, as well as sensory, impairment is present. Likewise, anal and vaginal winking were not elicited by prick of the ipsilateral thigh and ischial tuberosity.

It should be pointed out, finally, that, despite the above deficits and the hypermetria of proprioceptive and visual placing and of hopping reflexes, the animal struck and batted accurately at a moving string with the affected forelimb.

B. Total destruction of one dentate nucleus with additional encroachment of the lateral aspect of the nucleus interpositus (one animal, 14 days survival; Fig. 22) showed in addition to the symptoms described above (IV A), the following defects of the ipsilateral limbs: (*a*) goose-stepping gait, (*b*) slight increase in extensor tone, and (*c*) serious misplacement of these legs while walking on elevated bars, with the characteristic oscillation of the interpositus lesion. By the end of the survival period no deficit was seen in walking on the floor; proprioceptive placing was brisker and less hypermetric, and the asymmetry of tone was barely perceptible. The deficit in walking on horizontal bars remained without improvement and resulted in frequent falls toward the side of lesion.

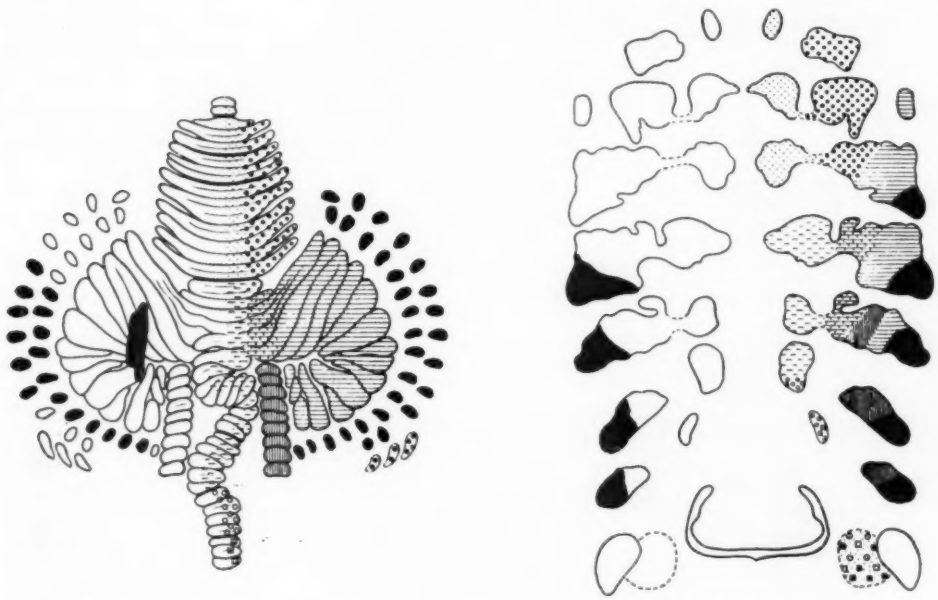

Fig. 23.—Schematic drawings of cerebellar cortex and nuclei, showing lesion (black) in the caudal lateral (paraflocculus) part of the dentate nucleus (left side of Figure).

C. Destruction of that part of the dentate nucleus to which the paraflocculus projects (one animal, 22 days' survival; Fig. 23)

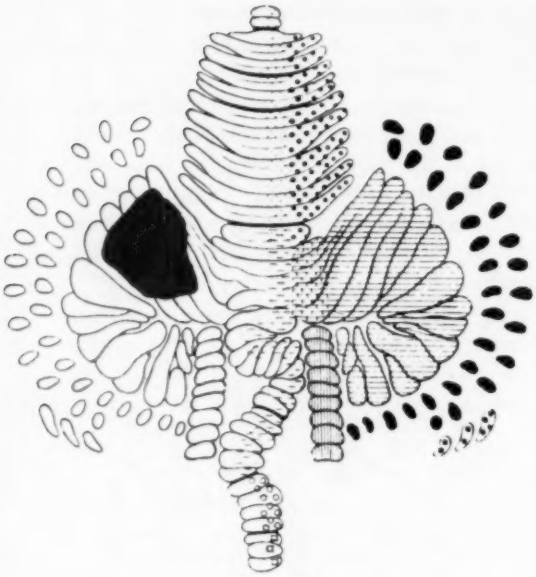

Figure 24

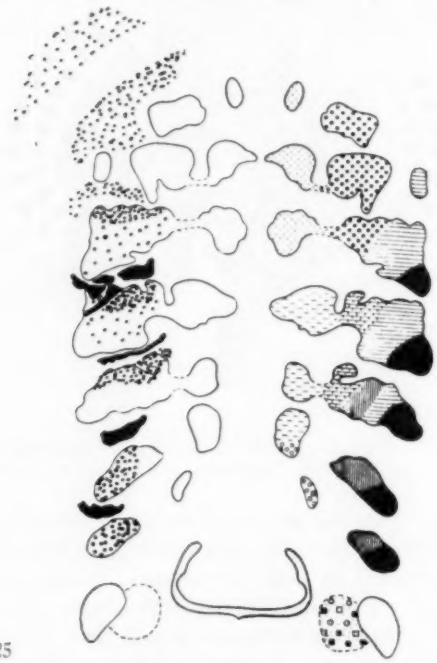

Figure 25

Figs. 24 and 25.—Schematic drawings of cerebellar cortex and nuclei, showing lesion (black) and gliosis (dots) in the cortex, Crus I, of the lateral zone (left side of Figure).

ible deficit in tone, posture, gait, or reflexes during a period of seven days after operation. Subsequent bilateral ablation of the sigmoid gyri caused no asymmetry in the symptoms following this lesion.

Similar cortical destruction in Crus I, but extending deeper into the white matter over the nucleus interpositus and the dentate nucleus with subsequent gliosis of those nuclei (one animal, 14 days' survival; Fig. 25) gave symptoms of a total interpositus lesion for the first three postoperative days, except that tactile placing was markedly reduced but not abolished in the ipsilateral foreleg. All deficits had disappeared by the fourth day except for slight symptoms of goose step, wrist instability, circumduction, and increase in supporting reflex of the ipsilateral limbs. There was also a mild misplacement of these legs when walking on elevated bars. By the 14th day no deficit in walking was present. Only the slightest asymmetry in supporting reflex and in mis-

resulted in no deficit except dilatation of the contralateral pupil.

D. Unilateral cortical lesion in Crus I (one animal, 22 days' survival; Fig. 24) without involvement of the nuclei showed no discern-

placement of the ipsilateral foreleg on the elevated was found. The contralateral pupil was slightly larger for the first time on this day.

COMMENT

The evidence for the physiological validity of longitudinal, vermal, and paravermal corticonuclear zones in the cerebellum of the cat has been presented in detail elsewhere (Chambers and Sprague [14]). The lateral longitudinal zone was not included in that paper, and the evidence for its function will now be discussed. It consists of the dentate nucleus and all cortex projecting to it, which in the cat includes Crura I and II and the paraflocculus (Jansen and Brodal [29]). In our hands, attempts to destroy the dentate nucleus unilaterally by stereotactic lesion have resulted in some involvement, gliosis, and perivascular cuffing of the closely adjacent nucleus interpositus. Two animals are described in this paper: One, which had mild interpositus involvement (Fig. 23), showed a typical interpositus syndrome, although the symptoms were milder and showed better recovery than following the interpositus lesion. The second animal, in which a small medial part of the rostral dentate was spared, and only slight involvement of the middle and caudal parts of the nucleus interpositus was found (Fig. 22), showed only that part of the interpositus syndrome involving placing and hopping reflexes and poverty of movement.

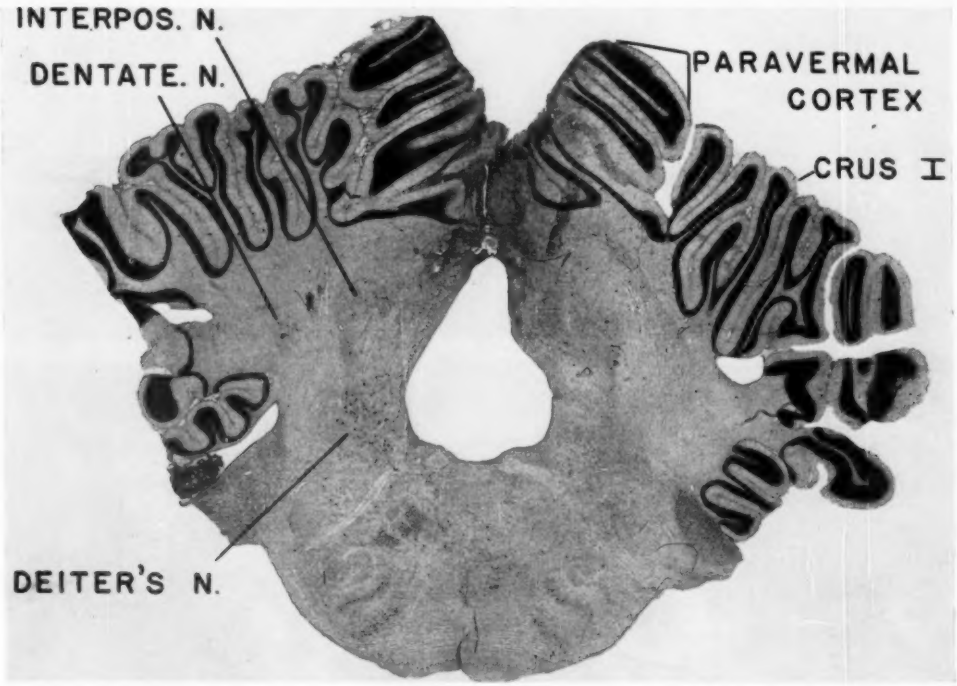

Fig. 26.—Photograph showing the extent of the bilateral lesion in the vermal cortex and fastigial nuclei, diagramed in Figure 5.

No deficit in tone or locomotion was discernible after the first few postoperative days. We must conclude that the dentate nucleus, or at least certain parts of it (that part to which the paraflocculus projects [Fig. 24] is not involved), shares with the nucleus interpositus the cerebellar control of placing and hopping reflexes and of voluntary movements.

Unlike the cortex of the paravermal and vermal zones, ablation of the cortex of the lateral zone (Crus I) was asymptomatic. No

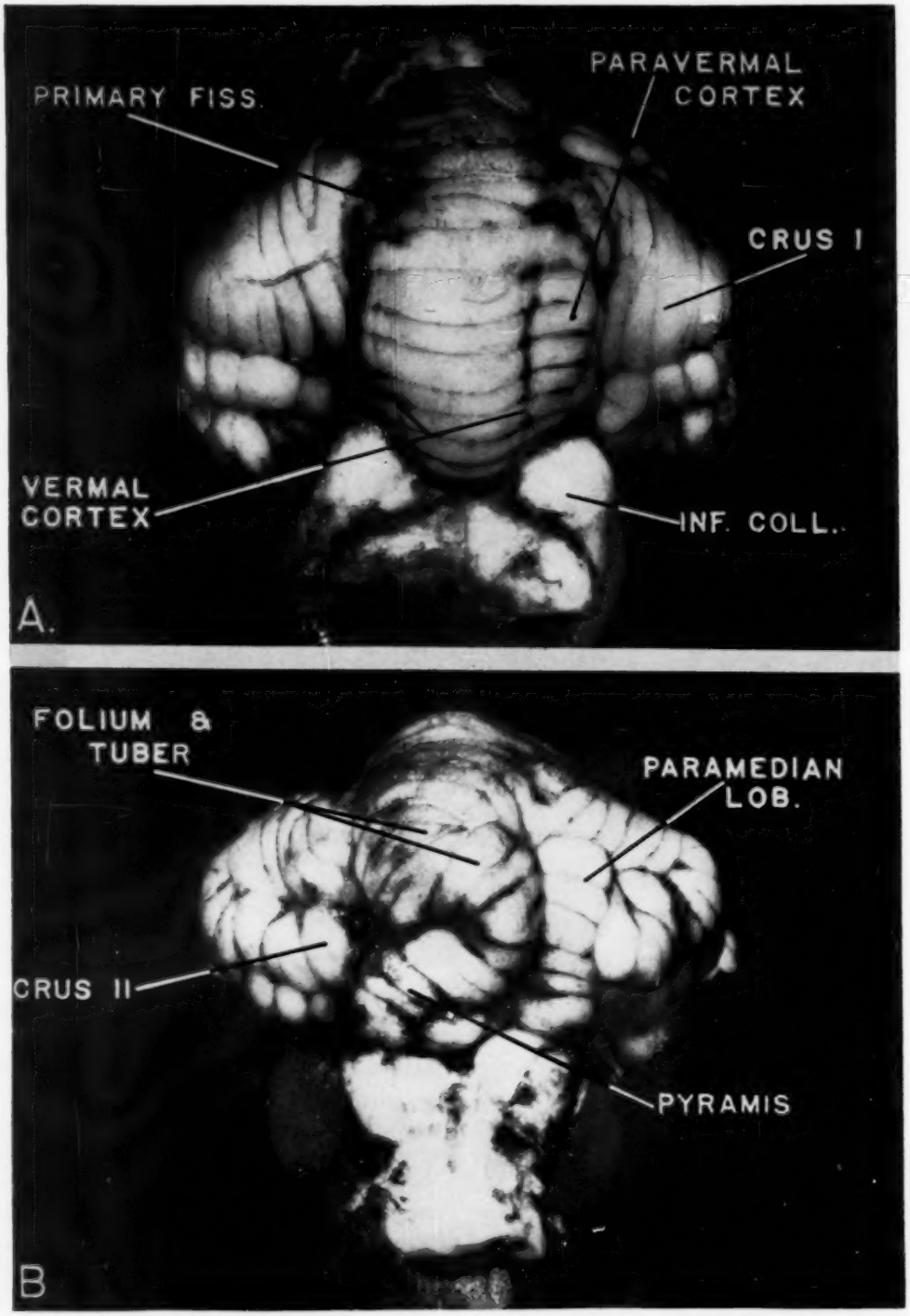

Fig. 27.—Photographs showing the extent of the unilateral ablations of the paravermal cortex in the anterior lobe (*A*) and in the paramedian lobule (*B*), diagramed in Figure 15.

asymmetry of posture, gait, or skilled movements became apparent when the sensorimotor cortices of the cerebrum were subsequently ablated, a procedure which altered and intensified in the monkey the symptoms of cerebellar lesion alone (Carrea and Mettler [12]).

These negative findings following cortical ablation of Crus I are opposed to the persistent reports in the literature of involvement (ataxia, asynergia, high step, disturbance of position sense, "weakness") of the ipsilateral foreleg (van Rynberk ‖; Ariëns Kappers, Huber, and Crosby[7]; André-Thomas[3]), based chiefly on the work of Bolk,[6] van Rynberk,[47] Pagano,[41] Grey,[22] Goldstein,[21] and Rothmann.¶ The later study of Ferraro and Davidoff [19] reported asynergia in both ipsilateral legs, especially the foreleg after ablation of Crus I. Most of these investigators did not supply histological evidence of the extent or specificity of their lesions. Lacking this, we are forced to conclude that their lesions in Crus I also involved the closely adjacent paravermal cortex of the anterior lobe, or extended deep enough to injure the rostral part of the nucleus interpositus. The infringement on the paravermal cortex would, according to our findings, result in ipsilateral flexion, while the deeper nucleus interpositus encroachment would give ipsilateral extension, both with accompanying asynergy. Similarly, hindleg effects following lesions in Crus II can be explained, in the absence of histological evidence to the contrary, by encroachment on the paramedian cortex or that part of the nucleus interpositus to which it projects. These assumptions are supported by the qualifications of several workers: Marassini,[36] Luna,[34] and Rothmann [44] maintain that only when the most medial parts of Crus I or II are involved do these lesions give the described symptoms in the fore- and hindlimbs, respectively. Vincenzoni [56] found no abnormality following ablation of the ansiform lobe in the goat, but subsequent extension of the lesion into the lateral simplex lobule brought out flexion and high step of the ipsilateral forelimb. Grey [22] found very mild and transient (two to five days) symptoms when his lesions of Crura I and II spared those medial parts bordering on the paravermal zone. Brinnert (cited by Grey [22]) emphasized the effectiveness of partial or superficial lesions in Crura I and II and specifically stated that high step of the ipsilateral foreleg only followed destruction of all parts of Crus I (i. e., including the most medial part). Keller, Roy, and Chase [31] found mild but transient symptoms in the dog and monkey after ablation of the cortex of Crura I and II and the paramedian lobule, as did Botterell and Fulton [8] and Carrea and Mettler [12] in the monkey; these workers denied any localization of the limbs in the ansoparamedian lobe, but their lesions were in no case specific enough to rule out this possibility. Rothmann [44] and André-Thomas and Durupt [5] both found localization of defects in the hindleg following lesion in Crus II in the monkey (André-Thomas [4]). We feel that the symptoms described by them were due to the involvement of the paramedian lobule and/or the nucleus interpositus.# Manni [35] likewise describes the changes in tone of specific limbs following localized lesions in the cortex of the crura of the guinea pig; in addition, he found alterations in the trunk. We cannot properly evaluate

‖ References 48 and 49.

¶ References 43 and 44.

André-Thomas [4] (1922) reported careful histological checks on unilateral lesions which attempted the destruction of the fastigial nucleus, and of the cortex of Crus II in two dogs, both of which were part of larger series described earlier by him.[13] The fastigial lesion was found to extend to the opposite nucleus fastigius and to injure the ipsilateral medial vestibular nucleus. The animal with a lesion in the ansiform lobe showed histological involvement of the dentate nucleus and the lateral part of the nucleus interpositus, as well as the superior folia of the paramedian lobule. In spite of this, André-Thomas considered that the remainder of his series of lateral lesions, undocumented histologically, demonstrated functional localization of the foreleg in the cortex of Crus I and of the hindleg in Crus II. These lesions, the surface extent of which was shown schematically, were even more medial in position than the one with histological verification.

the effects of his lesions, which were different from ours, because the nuclear projections of the various parts of the cortex are not known in this animal. It appears from his figures that his "crural" lesions included not only the lateral but also the paravermal zone, and apparently in some cases the vermal cortex as well.

Finally, it should be pointed out that, according to the concept of cerebellar organization proposed in the present paper and in that of Jansen and Brodal,* the paramedian lobe and the ansiform lobe should not be considered together. Total removal of one paramedian lobule resulted in symptoms similar to, but milder than, those following a lesion of the paravermal cortex of the anterior lobe, and in one animal they disappeared after 14 days. Similar results were obtained by Ferraro and Davidoff [19] and by Mussen,[59] also in the cat, although no histological data were given by them. Grey [22] reported (in the dog) no effects in the limbs but only transient (two to three days) pleurothotonos to the side of the paramedian lesion. Similar observations were made in the dog by van Rynberk,[47] who described forced rolling and pleurothotonos. Neither Grey nor van Rynberk made histological studies, but it appears to us certain, on the basis of our work, that their lesions extended beyond the paramedian lobule into the closely adjacent fastigial nucleus, in the case of the former, and into the vestibular nuclei, in the latter.

SUMMARY

This paper supports the concept of functional organization of the cerebellum in longitudinal, corticonuclear zones and is opposed to that theory which localizes function in the various lobes defined by comparative and embryological data.

The previous evidence of functional organization, obtained by stimulation and ablation, has been interpreted chiefly on the basis of the distribution of cerebellar afferent systems. The present concept emphasizes the efferent projections, originally defined anatomically by Jansen and Brodal.† Their specific corticonuclear connections, described in Marchi studies, are supported by selective nuclear gliosis following cortical lesions seen in Nissl preparations (Figs. 6, 7, 15, 18, 20, and 21).

The vermal zone consists of two contiguous, but independent, halves, composed of cortex and fastigial nucleus, each of which controls the posture, tone, locomotion, and equilibrium of the entire body and functionally resembles closely the extrapyramidal portion of the cerebrum. No qualitative difference exists between the symptoms following ablation of the vermal cortex of the anterior lobe and the rostral one- half of the fastigial nuclei and those following the ablation of the posterior lobe of the vermis (and nodulus) and the caudal one-half of the fastigial nuclei. Somatotopic localization is present in the vermal cortex, with maximal involvement of the tail in the lingula; hindlegs and pelvic girdle, in the centralis and rostral cumen; forelegs, pectoral girdle, head, and neck, in the caudal culmen; head, neck, and forelegs, in the simplex, and head, neck, and eyes in the tuber and folium. However, the entire body was involved to a less pronounced extent in each lesion. Localization in the fastigial nucleus had a similar orientation, but its minimal representation was limited to the fore- or hindparts of the body.

Vestibular function is not limited to the flocculonodular lobe, but is a function of the entire vermal zone. The vermis is an anatomical unit, based on its efferent connections, and a physiological unit, based on its electrical stimulation and ablation.

Each paravermal, intermediate zone, consisting of paravermal cortex and nucleus interpositus, controls the postural placing and hopping reflexes, tone, and individual movements of the ipsilateral limbs, and functionally resembles the pyramidal part of the cerebrum. The function of this zone is similar in the anterior and the posterior lobe, being quantitatively greater in the former except that the regulation of tactile placing is a property of the anterior lobe only. Somato-

* References 29 and 30.

† References 29 and 30.

topic localization in the cerebellum reaches its greatest discreteness in the paravermal cortex, especially that in the anterior lobe.

The cortex of the lateral zone in the cat does not appear to be involved in the regulation of posture or progression, whether this is tested by cerebellar lesion alone or such a lesion combined with destruction of the sensorimotor cortex of the cerebrum. The postural function of the dentate nucleus is limited at most to a regulation of placing and hopping reflexes and volitional movements of the ipsilateral limbs. No somatotopic localization was found in the lateral zone, although it has not been exhaustively explored.

The inclusion of the so-called middle lobe vermis (tuber and folium) and the paramedian lobule with Crura I and II as a functional unit is strongly opposed by the evidence presented here. The tuber and folium belong with the vermal zone; the paramedian lobule belongs with the paravermal zone. Likewise, the anterior lobe cannot be referred to as a single functional unit, nor can it properly be termed vermis alone.

The symptoms obtained from the nuclei of the vermal and paravermal zones are the reciprocal of those characteristic of their respective cortices. This reciprocality was obvious following even small cortical and nuclear lesions, which show precise somatotopic localization. This observation appears to demonstrate beyond question that these nuclei have both an afferent supply and a function independent of the cerebellar cortex.

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Effect of Cortisone and Hydrocortisone on Piarachnoid Adhesions

An Experimental Study

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It has previously been shown in acute and chronic experiments that cortisone can be administered repeatedly in certain doses into the cisterna magna of cats with safety.[1] As a continuation of these experiments, we have investigated the effect of cortisone and hydrocortisone administered intracisternally on the formation of experimentally produced piarachnoid adhesions.

Since the first report [2] on the depressing effect of cortisone on the formation of connective tissue, numerous investigations have been carried out that have confirmed these findings. It has been shown that this hormone was able to inhibit the formation of experimentally produced peritoneal,[3] pericardial, and pleural [4] adhesions in animals. However, there is only one report on the effect of adrenocortical hormones on experimentally produced piarachnoid adhesions.[5] In the present paper the effect in cats of adrenocortical hormones on piarachnoid adhesions produced by intracisternally administered talcum is described.

METHODS AND MATERIALS

Forty-seven cats on a free diet and weighing between 2 and 4 kg. were used. Cisternal punctures were performed with the animals under ether anesthesia and under sterile conditions. A sterile well-ground talcum suspension in saline containing 250 mg. per cubic centimeter was used. Fifty milligrams of this substance per kilogram of body weight was introduced slowly into the cisterna magna after a small skin incision had been made to facilitate the penetration of the needle. After the introduction of the talcum the cisternal fluid was aspirated and reinjected two or three times in order to obtain a uniform dispersion of the suspension. Twenty-two animals served as controls; 11 received repeated intracisternal injections of cortisone acetate, and 14, of hydrocortisone acetate,* every two or three days. Hormone injections were started on the seventh day after the administration of talcum and were continued till the end of the experiment. Each injection contained between 2 and 3 mg. of the hormone per kilogram of body weight, as these doses were found to be innocuous when given intracisternally.[1] In two animals the treatment with hydrocortisone and cortisone was stopped on the 25th and 30th days, respectively, following the introduction of talcum, and both cats were killed on the 43d day of the experiment. After an animal died or was killed, the whole brain except for the olfactory lobes, together with the first 3 cm. of the cervical spinal cord, was fixed in 5% neutral formalin for at least three weeks. For histological examinations paraffin sections from the spinal cord and various parts of the cerebrum were stained with hematoxylin and eosin and with Foot's or Laidlaw's method for reticulin. In addition, for comparative studies of treated and nontreated animals, a standard section was selected from each brain. This consisted of a 2-mm.-thick slice cut along the median line of the brain stem and included the interpeduncular cistern, pons, and medulla with their corresponding piarachnoid. The number of days of survival following the introduction of talcum and the number of injections of the hormone given each animal are shown in the accompanying Table.

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Effect of Adrenocortical Hormones on Piarachnoid Adhesions

Survival Period, in Days, Following Intracisternal Injection of Talcum	No. of Intracisternal Injections of Hormone *
Hydrocortisone	
9	1
10	1
12	2
14 (4 cats)	3
15	3
15	4
16	3
17	5
22	6
28	7
43 (treated up to 25th day)	7
Cortisone	
10	2
12 (2 cats)	2
13	2
13	3
16	3
17	4
27	7
30	8
30	9
43 (treated up to 30th day)	6

* Treatment was started on the seventh day following talcum administration; each injection contained between 2 and 3 mg. of the hormone per kilogram of body weight.

RESULTS

No particular reactions were observed in the majority of animals during the introduction of the talcum or injection of the hormone intracisternally; in a few cases only the animal jerked when the needle was introduced into the cisterna magna. Usually the animal recovered quickly from the ether anesthesia. No obvious neurological disturbances were observed during the period of the experiments, but the animals which died became drowsy a few days before death.

Macroscopic Findings in Nontreated and Treated Animals

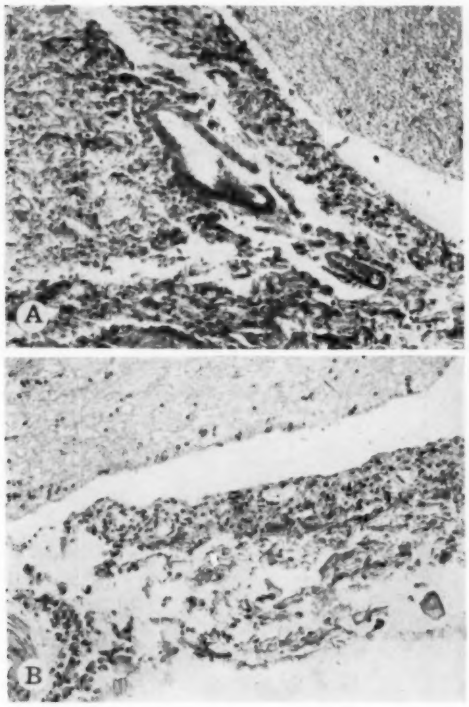
In all animals, treated and nontreated, the main mass of talcum powder injected was found within the subarachnoid space along the basal surface of the brain stem. Some talcum was seen in the cisterna magna, as well as within the subarachnoid space of the portion of cervical cord examined. Over the convex surfaces of the cerebral hemispheres the meninges were translucent and glistening in all cases except two, which had purulent meningitis, and these were therefore excluded from further study. Internal hydrocephalus was not found in either the treated or the nontreated animals during the observation period.

Microscopic Findings

Nontreated Animals. — In five animals killed six, seven, and eight days after the talcum injection the histological picture was identical. The piarachnoid space was distended by the presence of talcum particles in large quantities lying free within the space. Some of them, adjacent to the pia mater, were surrounded by histiocytes having small, pyknotic nuclei and scanty, eosinophilic cytoplasm. In these areas a mild to moderate infiltration with polymorphonuclear cells and lymphocytes was also present. In one case there were a few small areas of severe acute inflammation with vasculitis and karyorrhexis of exudative cells. With special stains a fine and scanty reticulum network along the pia mater was revealed, with short twigs hanging over into the subarachnoid space.

Fig. 1.—Piarachnoid seven days after introduction of talcum, just before treatment was started. All talcum particles are lying free within the piarachnoid space. Along pia (top) a mild inflammatory reaction is seen. Hematoxylin-eosin stain; × 140.

In brief, the pathological state on the seventh day after talcum administration, just before treatment with either cortisone



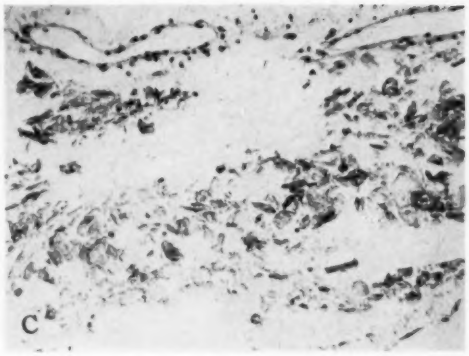


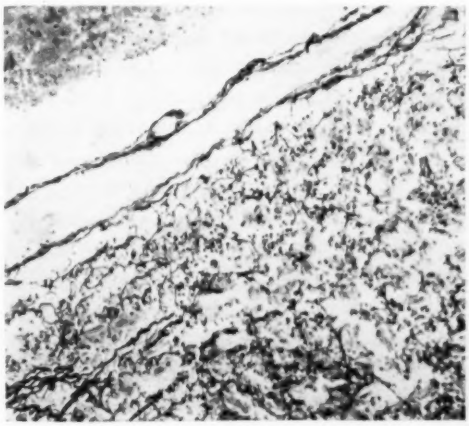
Fig. 2.—*A*, 15-day nontreated animal. Most talcum particles are surrounded or engulfed by histiocytes. Hematoxylin-eosin stain; × 140. *B*, 16 days; treatment with cortisone. Most talcum particles are lying free within the piarachnoid space. Along the pia some particles are surrounded or phagocytosed by histiocytes. Hematoxylin-eosin stain; × 140. *C*, 15 days; treatment with hydrocortisone. Almost all talcum particles are lying free within the subarachnoid space. Few histiocytes and lymphocytes are seen around the blood vessels. Hematoxylin-eosin stain; × 140.

or hydrocortisone was started, was the presence of a mild acute inflammation in the piarachnoid membrane of the cats, while histiocytes were just making themselves apparent around talcum particles nearest to the pia (Fig. 1). Identical histological findings were found on the sixth and on the eighth day.

From the eighth day onward the histological picture in the nontreated animals was one of progressive accumulation of histiocytes within the subarachnoid space, as well as an increased rate of phagocytosis of the talcum particles. On the 15th day almost all particles were within macrophages, many of them of the foreign-body giant-cell type (Fig. 2*A*). By the 19th day all particles were surrounded within the subarachnoid space by poorly vascularized foreign-body granuloma-like tissue, including some fibrocytes. This tissue formed dense adhesions between the pia and the arachnoid. The accumulation of histiocytes was accompanied by progressive spread of the reticular network throughout the whole length and width of the space (Fig. 3). Precisely the same lesions as those seen on the 19th day were found in the control animals that survived for 23, 27, 35, and 43 days, respectively (Fig. 4*A*). A moderate inflammatory reaction was observed in the leptomeninges in all animals.

Treated Animals. — In cortisone-treated, and particularly in hydrocortisone-treated, animals a definite retardation in the process

Fig. 3.—Control, 22 days. The reticulum network follows pattern of distribution of histiocytes. Laidlaw's reticulum stain; × 140.



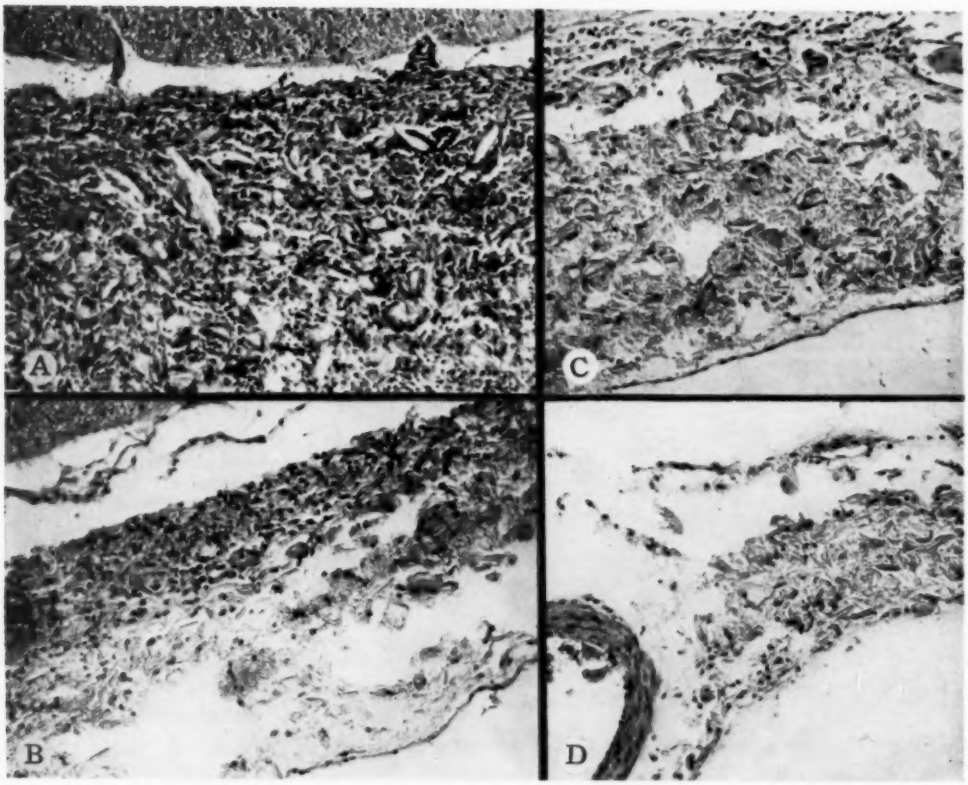


Fig. 4.—*A*, 30-day control. All talcum particles are phagocytosed by macrophages, many of them of the foreign-body giant-cell type. Hematoxylin-eosin stain; reduced to 80% of mag. × 140. *B*, 30 days; treatment with cortisone. Along the pial side of the piarachnoid talcum particles are either surrounded or engulfed by histiocytes. Many particles are still lying free within the piarachnoid space. Hematoxylin-eosin stain; reduced to 80% of mag. × 140. *C*, 22 days; treatment with hydrocortisone. Most talcum particles are lying free within the subarachnoid space. Some of them adjacent to the pia (top) are surrounded or phagocytosed by histiocytes. Hematoxylin-eosin; reduced to 80% of mag. × 140. *D*, 28 days; treatment with hydrocortisone. Almost all talcum particles are lying free within the subarachnoid space. Hematoxylin-eosin stain; reduced to 80% of mag. × 140.

of histiocytic migration, phagocytosis, and subsequent organization of the talcum particles in the subarachnoid space was observed.

Thus, while on the 15th day almost all talcum particles in the control animals were either surrounded or engulfed by macrophages, in cortisone-treated animals on the 16th (Fig. 2*B*), and even on the 17th, talcum day many of the particles were still lying free within the subarachnoid space, while others had histiocytes attached to them, the latter showing only slight phagocytic activity. Up to the 30th day after talcum administration (Fig. 4*B*), a histological picture was observed in the piarachnoid of cortisone-treated animals very similar to that seen on the 15th day in the controls. A reticulin network in cortisone-treated animals appeared wherever there were histiocytes and macrophages and closely followed the pattern of distribution of these cells within the piarachnoid. No morphological differences were found in the reticulin and in the inflammatory reaction of the leptomeninges between the control and the cortisone-treated animals.

In the animals which received hydrocortisone and were killed on the 15th day following talcum administration (Fig. 2*C*), the histological picture in the leptomeninges was very similar to that observed on the 7th

day in the controls, that is to say, just before the animals were placed under treatment. In other words, hydrocortisone blocked for eight days the leptomeningeal reaction to talcum in the state it was in when it was first injected. Up to the 22d (Fig. 4*C*) and the 28th (Fig. 4*D*) day after introduction of talcum the particles were still lying free within the subarachnoid space, while others close to the pia were surrounded or engulfed by macrophages, none of them of the foreign-body giant-cell type. Almost no reticulum network appeared in these animals (Fig. 5). The inflammatory reaction was found to be less conspicuous than that in either the control or the cortisone-treated animals.

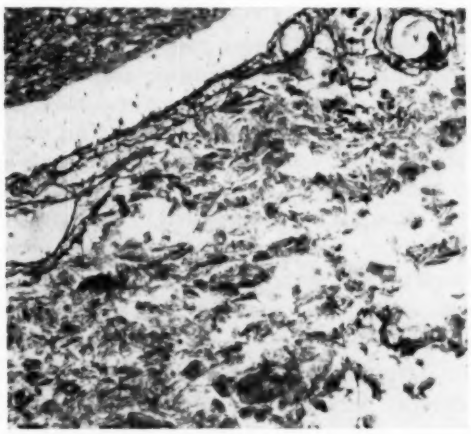


Fig. 5.—Twenty-two days; treatment with hydrocortisone. Reticulum network follows pattern of distribution of histiocytes (cf. Fig. 4*C*). Laidlaw's reticulum stain; × 140.

The two animals, one treated with hydrocortisone and the other with cortisone, which remained without treatment for 18 and 15 days, respectively, were killed on the 43d day of the experiment, and presented an entirely different histological picture. While in the hydrocortisone-treated animal the changes were similar to those observed on the 22d day in another animal treated with hydrocortisone continuously (Fig. 4*C*), the picture in the cortisone-treated animal was similar to that seen in a nontreated control killed after 30 days (Fig. 4*A*).

COMMENT

It is evident from the present investigation that cortisone and, especially, hydrocortisone inhibit the development of adhesions in the subarachnoid space. This inhibition was apparently not due to any factor operating during the first, or exudative, phase, which preceded the productive, or histiocytic, phase. In fact, it was in order to avoid such a possibility that treatment was begun at the start of the productive phase. We were interested in assessing the effect of the adrenocortical hormones on the factors which were directly responsible for the development of adhesions. By so doing, we wanted, furthermore, to prevent the mechanism of histiocytic release from having a priori conditions different in the treated and in the nontreated animals. The administration of the adrenocortical hormones was started on the seventh day after talcum administration, as our histological studies showed consistently that in the leptomeninges of cats it is on the sixth or seventh day after injection of talcum that the initial exudative reaction is lowest, while the second, i. e., the productive, phase, is just starting to become evident.

Impairment of macrophagic migration and activity in cortisone-treated animals in cutaneous tissue,[6] as well as in the peritoneal[7] and pleural[8] cavities, has been reported by a number of observers, and a similar effect was obtained with the topical application of the hormone.[9] Recent studies with radioactive substances have shown that the phagocytic function of the reticuloendothelial cells in mice is depressed by small doses of cortisone.[10] In our experiments the adrenocortical hormones inhibited principally the release of histiocytes, as well as their phagocytic activity. Cortisone decreases vascular permeability,[11] thus impairing the migration of inflammatory cells and consequently reducing the local phagocytic activity. Furthermore, the primary destructive effect of the adrenocortical hormones on the lymphocytes is well known, and as these cells, which probably constitute the source of tissue macrophages, are reduced,[6] there is obviously a major

reduction in the number of macrophages, and consequently inhibition of the formation of foreign-body giant-cell granulomata, which formed the piarachnoid adhesions in our experiments.

The effect of the adrenocortical hormones on mesodermal elements is a direct one and is not mediated by way of a systemic mechanism causing nitrogen loss from the body. This effect has been shown both in the topical application of the hormones in cutaneous lesions [12] and in experimental peritoneal adhesions.[13] In addition, in tissue culture studies, it has been demonstrated that hydrocortisone causes considerable and selective growth inhibition of fibroblasts and that it is much more effective in this respect than cortisone.[14] In other experiments cortisone has been shown to inhibit the growth of both fibroblasts and macrophages in vitro.[15] This topical effect of adrenocortical hormones is well demonstrated by their favorable action when introduced intra-articularly in cases of rheumatoid arthritis. When the effects of cortisone and hydrocortisone are compared, a marked superiority in intensity and duration of activity is shown by the latter. The clinical improvement, as well as the effect on joint temperature, has demonstrated that hydrocortisone acts only locally, and not as a result of its absorption into the blood from the synovial space, as the antiphlogistic effect was observed in the injected joint only.[16] In our experiments as well, hydrocortisone had a much greater effect than cortisone on the meningeal reaction, and, though nothing is known about the absorption of adrenocortical hormones from the subarachnoid space, it can be assumed that the effect was local, especially in view of the slight solubility of hydrocortisone acetate. The fact that hydrocortisone had a much longer action than cortisone, as seen in the two animals in which the treatment was stopped more than two weeks before the end of the experiment, also indicates that the hydrocortisone crystals probably remain longer in the subarachnoid space than those of cortisone. Studies on the fate of intra-articularly administered cortisone acetate and hydrocortisone acetate have revealed that the latter is found in greater concentration in the synovial cells than is the former.[17] Hydrocortisone is also much less soluble than cortisone in body fluids, and thus probably diffuses less rapidly from the site of local action. These facts, as well as the evidence that hydrocortisone is the principal hormone secreted by the adrenal cortex,[18] may explain its superiority when applied directly to the tissues.

When the hormone is administered systemically in doses sufficient to suppress inflammation and, subsequently, connective tissue formation, there is also a general metabolic influence, whose side-effects may be deleterious, especially if the treatment is continued for some time. On the other hand, possibly by direct application of relatively small doses of hydrocortisone acetate, a high concentration of the hormone may be obtained in a limited area, which will have an effect similar to, and even greater than, that produced by systemic administration. Such a concentration has probably been achieved in our experiments, as suggested by the marked inhibition of the meningeal reaction in the subarachnoid space and the prevention of the formation of adhesions.

While these experiments were in progress, Oppenheimer and Riester [5] reported the effect of intramuscular cortisone on the formation of piarachnoid adhesions produced by talcum in rabbits. It was shown that this treatment during 15 days caused inhibition of piarachnoid adhesions, as compared with control animals. The rabbits under treatment lost weight considerably and became markedly lethargic and emaciated, owing to the systemic effect of cortisone. In two animals two consecutive intracisternal injections of hydrocortisone caused some diminution of meningeal reaction. These animals did not show, however, the systemic effect observed in the cortisone-treated animals. Though Oppenheimer and Riester reported that intracisternal administration of talcum and hydrocortisone in rabbits caused striking convulsive behavior and extensor rigidity, no such complications were observed in the pres-

ent experiments. As reported previously,[1] no deleterious effects were observed when cortisone was administered repeatedly in small doses into the cisterna magna of cats.

It was impossible to compare the survival rate of treated and nontreated animals as an index of the efficiency of therapy, since in both groups the subarachnoid space was filled with talcum particles, which undoubtedly interfered seriously with the CSF circulation. The repeated anesthesias and cisternal punctures probably also contributed to the early death of a number of treated animals.

The results of our previous and present investigations permit an evaluation of the possible use of the adrenocortical hormones in the prevention of piarachnoid adhesions. Recently, clinical studies have been reported in which cortisone systemically and hydrocortisone intrathecally were used in combination with antituberculous drugs in the treatment of tuberculous meningitis.† This treatment, when given early, seemed to inhibit the formation of piarachnoid adhesions, and subsequently of subarachnoid block, thus overcoming one of the most important complications and dangers to life in this disease. In patients suffering from tuberculous meningitis in the Children's Hospital in Helsinki,[21] cortisone was given by mouth and hydrocortisone was introduced by intralumbar injection, suboccipitally, and intraventricularly, without apparently any untoward effects, and the impression was gained that this treatment prevented mechanical obstruction of the CSF circulation and shortened the period of treatment. Our experimental data bring direct evidence that in fact the formation of piarachnoid adhesions can be inhibited by the early intrathecal administration of adrenocortical hormones. This finding, as well as the recent clinical observations [22] that hydrocortisone in certain doses when administered by the intralumbar or the suboccipital route, is tolerated perfectly well and does not cause any damage to the organism, seems to us to be of considerable practical importance.

† References 19 to 21.

There are other causes of adhesive arachnoiditis besides tuberculous meningitis for which there is no treatment and which may cause severe pathological changes in the central nervous system, and even death. It is suggested that hydrocortisone should be administered intrathecally early in such cases, as well when there is evidence of a progressive process, and especially when systemic administration of adrenocortical hormones may be contraindicated.

SUMMARY

The effect of intracisternal cortisone and hydrocortisone on the formation of talcum-induced piarachnoid adhesions was investigated in cats. In the nontreated animals dense adhesions were formed. Repeated intracisternal administration of cortisone and, especially, of hydrocortisone at intervals of two or three days in 25 animals decreased mainly the migration and phagocytic activity of the histiocytes in the subarachnoid space, and thus inhibited the formation of foreign-body giant-cell granulomata, which formed the piarachnoid adhesions in the nontreated animals.

The practical application of these findings is discussed, and it is suggested that intrathecal hydrocortisone be tried in pathological conditions of the central nervous system which are associated with the formation of piarachnoid adhesions.

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Abstracts from Current Literature

EDITED BY DR. BERNARD J. ALPERS

Physiology and Biochemistry

THE EXPERIMENTAL ANATOMOPHYSIOLOGIC APPROACH TO THE STUDY OF DISEASES OF THE BASAL GANGLIA. F. A. METTLER, J. Neuropath. & Exper. Neurol. **14**:115, 1955.

Mettler presents his thesis that many neurologic disorders and some of the diagnostic categories of psychiatry are complexes, rather than entities, and are precipitated by a potentially variable pathophysiology. He further suggests that, instead of the search for a "cause" of a number of these illnesses, more profit might be obtained from the analyses of the basic physiologic distortions.

Certain factors must be kept in mind during such an analysis: (1) factors of safety; (2) substitution of inferior function, wherein the organism adapts to an altered state; (3) integrative action, which implies that the frame of reference obtained when a particular system is being tested may determine what the function of that system is, and (4) algebraic summation, in which, in general, it is noted that neural lesions summate not in arithmetical, but in algebraic, manner, so that the addition of two lesions is greater than the sum of what is seen when they occur separately (principle of supramaximal summation), or a second lesion may be of such a nature as to offset the nature of the first (principle of negating summation).

Mettler states that ataxia is admittedly due to interference with the cerebellum or of its afferent or efferent pathways, although the extent to which some such phenomena may be present is a subject which requires some clarification. In regard to simple tremor (rest tremor), he summarizes some conflicting views and states that simple tremor, like ataxia and ataxic (intention) tremor, is the consequence of interference with cerebellar apparatus. Simple tremor is the consequence of interference with the analogue of the brachium conjunctivum posterius, or the caudal projection of the superior cerebellar peduncle. Ataxic tremor is due to damage of the brachium conjunctivum anterius, or the rostral projection of the superior cerebellar peduncle, through the cerebellothalamic and cerebellopallidal projections.

In discussing chorea, choreoid activity, ballism, and athetosis, Mettler notes the difficulty in clearly defining these phenomena and the overlap among them. In this group of disorders, the correlation between pathologic findings and the clinical picture is reasonably definite for ballism and for athetosis. In the former, damage to the nucleus Luysi is seen. Hyperkinetic phenomena are usually associated with supratentorial lesions involving the fibers of the brachium conjunctivum.

Hypokinesis may be due to loss of mechanisms required for associated movements, as in damage (or reversible dysfunction) to the pallidum, substantia nigra, or red nucleus; to impairment of the conditions necessary for the freedom of movement, as in the development of rigidity, or to a loss of drive, which may result from reduced focalized sensory irradiation of the motor system.

Spasticity consists in increased sensitization of myotatic reflexes to proprioceptive stimulation. Rigidity may profitably be regarded as an abnormal bombardment of the myoneural outflow by vestibular or proprioceptive influences due to the release of impulses from the vestibular nuclei themselves or the pallida, or at levels between the pallida and the cortex, including the latter, such as may occur in cerebral palsy.

Mettler suggests that in paralysis agitans, because of the natural variability in the clinical conditions, there is damage to several systems, which for some reason may be involved simultaneously. Approaching the problem from this point of view, he notes that a satisfactory structural basis for each of the individual elements in the disease complex can be established. Thus, damage to the fibers which lie in the ventral part of the brachium conjunctivum, and which progress between the red nucleus and substantia nigra to the zona incerta, and thence to the thalamus and globus pallidus, results in simple tremor, the type generally considered characteristic of paralysis agitans. When ataxic tremor is present, involvement of the fibers in the dorsal two-thirds of the brachium conjunctivum is to be expected, and intrinsic cerebellar or more generalized lesions should be considered, a circumstance which should lead to a guarded prognosis and which very

probably is a contraindication to surgical intervention. A marked degree of rigidity occurs only with lesions at supratentorial levels when there is abnormality in the internal capsule or in such location as to involve both corticifugal and extrapyramidal fibers. Paucity of movement may arise either as the consequence of rigidity or because of true hypokinesia due to loss of pallidal function. Vegetative disorders, similarly, may arise from hypothalamic dysfunction or interference with pathways entering or leaving this structure.

It is noted that the mechanisms concerned lie in a rather small area which has as its center the apex of the pallidum and includes the tegmental fields of Forel, projections of the pallidum and adjacent internal capsule, and subthalamic decussation. This is one of the regions which is involved by encephalitis, and which presents certain peculiarities of vascular supply, transitional between the basilar and the carotid arteries, and specifically supplied by the posterior communicating arteries.

SIEKERT, Rochester, Minn.

SEIZURE PATTERNS INDUCED BY ELECTRICAL STIMULATION OF HIPPOCAMPAL FORMATION IN THE CAT. O. J. ANDY and K. AKERT, J. Neuropath. & Exper. Neurol. **14**:198, 1955.

Andy and Akert report observations on the hippocampal formation in cats. The low convulsive thresholds for mechanical stimulation, lower than any other part of the brain, and for electrical excitation, about as low as, or lower than, the motor cortex, were noted. Simple insertion of electrodes into the hippocampus may elicit a sudden burst of electrical activity, called "injury discharge," which can develop slowly into a well-differentiated and synchronized discharge pattern, spreading to cortical and subcortical structures. Electrical stimulation of the cornu ammonis produces a characteristic EEG discharge pattern, the predominant feature of which is a train of high-frequency and high-amplitude spikes. The propagation of the discharge is most pronounced in the limbic system. However, frontal, parietal, and temporal association areas are also involved, whereas the primary sensory and motor areas are spared. The function of the motor and sensory systems appears unaltered during the discharge in the cornu ammonis, since there were adequate and appropriate reactions to visual, auditory, and nociceptive stimuli. Pentobarbital (Nembutal) anesthesia raises the threshold of this electrically induced after-discharge and decreases its duration.

The lack of conspicuous change in behavior of a cat on electrical stimulation of the hippocampal formation was in marked contrast to the impressive changes in the EEG. No motor discharge, no change of muscle tone, and no overt alteration in behavior occurred as long as the after-discharge was confined to hippocampal formation. But with spread of the after-discharge to other structures, the spontaneous behavior was altered. When the discharge, propagated throughout the limbic system, projected upon the association areas of the cerebral cortex, the animal ceased its spontaneous activity, such as lapping milk, and stared or looked around in apparent bewilderment. The arrest occurred a few seconds after the onset of the discharge and may have been resolved a few seconds before the cessation of the electrical activity. When the after-discharge from the limbic system extended to the motor and sensory cortical areas, with the use of more current, a major convulsion could be produced. During a hippocampal discharge alone, the cat was indifferent to a mouse but attacked as soon as the seizure was completed. Some autonomic responses, such as change in respiration, blood pressure, and pupillary size, were also observed during these after-discharges.

SIEKERT, Rochester, Minn.

EFFECTS OF CHANGES IN TEMPERATURE ON REACTIONS OF SPINAL CORD. C. McC. BROOKS, K. KOIZUMI and J. L. MALCOLM, J. Neurophysiol. **18**:205, 1955.

In addition to the well-known blocking actions of heat and cold on cord activity, it has been found that augmentation of response occurs as temperatures are altered. The mechanism whereby cooling produces these increases in response is not thoroughly understood. Studies were carried out to determine the effects of changes of cord temperature on the various potentials evoked in association with certain types of reflex activity. Progressive cooling of the spinal cord produced first an increase in amplitude and duration of potentials recorded from the cord surface and the dorsal and ventral roots; but after a critical level was reached, these potentials were reduced in magnitude and block ensued. Heating the cord above normal progressively reduced the size of the potentials. The cold-induced hyperactivity was not due to hyperexcitability of cord elements, because thresholds to direct stimulation were increased. Intramedullary conduction of

impulses was slowed by cooling and the excitatory processes at synaptic junctions were retarded in development, but the "synaptic potentials" resulting were of greater amplitude and duration. A lowered excitability of motor neurons was suggested.

The cold-produced augmentation of the dorsal-root and ventral-root reflex discharge was greater than that of the afferent volley. This was ascribed to increase in magnitude of potentials in intramedullary elements and to the greater duration of excitatory processes. It was noted that as cooling occurred, the threshold of the dorsal and ventral roots to direct stimulation was raised. The results of certain experiments indicated that neither cooling nor heating increases the electrical excitability of nerve cell bodies or fibers. Since the thresholds were found to be raised, it was felt that augmentation of response obtained on cooling cannot be due to an intrinsic or induced hyperexcitability of the cord elements.

It was found that when an action potential initiated by stimulation of a peripheral nerve reached a cool segment of the dorsal root adjacent to a cooled spinal cord, it increased in amplitude and duration, indicating that the stimulus delivered at the central synapse is much more potent than that delivered at normal body temperatures. At supernormal temperatures there appeared to be no diminution in the afferent volley at a time when the efferent potentials picked up from the roots and the cord began to decrease in amplitude and duration. The hyperresponsiveness on cooling is explainable on the basis of amplification of the excitatory action of each single neural element, for it was noted that monosynaptic reflexes were not increased to as great an extent as were the polysynaptic reflex and the dorsal root reflex.

SIEKERT, Rochester, Minn.

CEREBRAL STRUCTURES INVOLVED IN TRANSMISSION AND ELABORATION OF NOXIOUS STIMULATION. J. M. R. DELGADO, J. Neurophysiol. **18**:261, 1955.

Protective reflexes, grimaces, and vocalization and autonomic manifestations appear in monkeys under the influence of noxious stimulation. Since these manifestations are associated with pain in humans, it may be supposed that similar sensations are experienced by animals. For the purposes of the present study, however, attention was directed mainly to the high-pitched vocalization and defensive-offensive movements. The aim of the investigation was to study some of the brain structures stimulation of which evokes these responses. The typical pattern consisted of (1) vocalization, a rhythmic succession of loud and high screeches; (2) facial grimacing, with retraction of the angle of the mouth, wrinkling of the face, contraction of both the upper and the lower lip, and retraction of the ear, all contralateral to the stimulated area of the brain; (3) defensive and offensive movements; (4) autonomic manifestations, such as pupillary dilatation and increased heart and respiratory rates, piloerection, urination, defecation, and salivation, and (5) conditioned anxiety. Elicitation of these responses a few times was found to induce signs of anxiety, which appeared the moment the animal was placed on the experimental stage and which consisted in attempts to escape, biting, and restlessness. Electrical stimulation of the lateral part of the tegmentum, the central gray matter, the posteroventral nucleus of the thalamus, the crus of the fornix, and the posterior part of the hippocampus elicited the typical pattern.

In the cat, electrical stimulation of the tectal area induced fighting against control animals, showing that the offensive reaction was purposive and well oriented. Stimulation of certain other areas of the brain, including the sensorimotor cortex, the middle and anterior portions of the cingulate gyrus and the pulvinar, the nucleus medialis dorsalis of the thalamus, the medial part of the tegmentum, and the frontal lobes between coordinates A-22 to A-27, did not produce this faciovocal response.

The thresholds to evoke vocalization were increased by the use of pentobarbital (Nembutal) sodium. Injection of acetylcholine into the tegmental part of the pons in the region of the spinothalamic tract lowered the threshold for the production of vocalization by stimulation of that area.

SIEKERT, Rochester, Minn.

OCCLUSION OF THE MIDDLE CEREBRAL ARTERY UNDER NORMOTENSION AND ANEMICALLY INDUCED AND CHEMICALLY INDUCED HYPOTENSION. B. RALSTON, T. RASMUSSEN, and T. KENNEDY, J. Neurosurg. **12**:26, 1955.

The authors report the extent of cerebral damage following occlusion of the middle cerebral artery in monkeys under various conditions of induced hypotension. In the normotensive group of animals studied, the middle cerebral artery was ligated and the blood pressure was maintained

by blood transfusion and dextran. This caused areas of softening in the head of the caudate nucleus, as well as the inferolateral portion of the cortex. Little damage was noted in posterior coronal sections. When hypotension was produced by bleeding of the animal, a far more extensive softening occurred than in the normotensive group. On the other hand, when Afronad, a thiophonium derivative, was used, a hypotension similar to that encountered with the methonium compounds was produced, which resulted in an infarct similar to that found in the normotensive group except that there was a greater degree of necrosis locally. This softening was far less than that seen in the anemically hypotensive animals. The mechanism of protection offered by Afronad is not known, although it may be related to a decreased cerebral blood flow.

The authors conclude that the benefits of increased safety provided by chemical hypotension outweighs the disadvantages of a slight increase in local tissue damage.

MANDEL, Philadelphia.

ROLE OF HYPOTHALAMIC MECHANISMS IN THALAMIC PAIN. E. A. SPIEGEL, M. S. KLETZKIN, E. G. SZEKELY, and H. T. WYCIS, Neurology **4**:739, 1954.

A number of clinical observations suggest that the hypothalamus may play a role in the genesis of the Dejerine-Roussy syndrome. Spiegel and his co-workers studied experimentally the effect of thalamic lesions upon the electrical activity of the hypothalamus and upon the evoked potentials led off from this area on sensory stimulation. Thalamic lesions were produced in the area of the ventral posterolateral nuclei. Two groups of experiments were performed—acute experiments, in 16 cats, and chronic experiments, in 10 cats.

For the development of thalamic pain ascending impulses entering the diencephalon are essential, since the thalamic pain disappears if the ascending systems passing through the midbrain are interrupted in sufficient extent that a definite hypalgesia results.

After elimination of the endings of the long afferent systems in the ventral posterior thalamic nuclei, there are three areas where pain impulses may be integrated: in the mesencephalon, particularly its tectum; in the hypothalamus, and in the cortex.

The sensory cortex develops isolation phenomena following a lesion of the ventral posterior nuclei but seems to play only an accessory role in the development of the thalamic syndrome, since its ablation does not abolish the thalamic pain. The cortical and mesencephalic integration of the pain impulses may play a part in determining the localization of the pain, but its tectal origin does not sufficiently explain certain features of the thalamic pain, such as its response to emotions and the associated vegetative disturbances.

The authors believe that the entrance of pain-conducting impulses into the hypothalamus plays an important role in the genesis of the Dejerine-Roussy syndrome. This view is supported by experiments showing that elimination of the ventral posterior thalamic nuclei is able to increase the potentials evoked in the hypothalamus by stimulation of afferent nerves.

ALPERS, Philadelphia.

LOCALIZATION OF BRAIN LESIONS BY MEANS OF RISA. J. A. RUSHTON, H. J. SVIEN, and E. J. BALDES, Proc. Staff Meet., Mayo Clin. **29**:478, 1954.

A total of 121 patients were studied with RISA (radioactive iodine in human serum albumin). Of this group, 37 were controls, and the remaining 84 had intracranial lesions. From the results of this study, Rushton and his colleagues conclude that this procedure, in its present stage of development, is not a useful method for localization of intracranial lesions.

ALPERS, Philadelphia.

Neuropathology

CYTOLOGY AND CELLULAR PATHOLOGY OF THE OLIGODENDROGLIOMAS OF THE BRAIN. J. R. HAVENS, L. L. ADAMKIEWICZ, and R. GROFF, J. Neuropath. & Exper. Neurol. **14**:142, 1955.

Ravens, Adamkiewicz, and Groff report on the examination of 39 oligodendrogliomas, particularly with regard to the cytology and cellular pathology of these tumors. The neoplastic oligodendrocytes can be regarded as cells which have not yet completed their differentiation. The cytoplasmic extensions do not serve as vascular foot-plates, nor do they exhibit intracytoplasmic fibrils and gliosomes. Several different types of neoplastic oligodendrocytes were encountered. The neoplastic cells more frequently encountered were cells which have a

resemblance to Types I and II of the normal oligodendrocytes of del Rio Hortega. Types III and IV of the normal oligodendrocytes (del Rio Hortega) were seen less frequently. According to the distribution of these neoplastic cells and the amount of mucoid interstitial substance, five types of oligodendrogliomas were recognized: diffuse, pseudoalveolar, loose, lacunar, and alveolar, each presenting a characteristic appearance. The types, however, were arbitrarily chosen and devised to facilitate the diagnosis of the tumor. In the opinion of the authors, there is but one principal type, the diffuse type, and the other forms are subtypes of it.

In these tumors, marked dilatation of the blood vessels, edema, hemorrhagic extravasation, and initial necroses were observed. The nerve cells in the central part of the tumor disclosed acute degeneration, while in the periphery the pathologic changes in the nerve cells varied in degree according to their nutritional status. Almost invariably hypertrophy of the remaining astrogliocytes was observed.

The neoplastic cells definitely in transition displayed two trends, one to the protoplasmic and the other to the fibrillary astrocyte. Nine of these 39 specimens were found to be oligodendrogliomas in transition. Those located in the gray matter or near the surface of the brain had a tendency to develop into the protoplasmic astrocyte form, while those in the white matter had a tendency to develop into the fibrillary astrocyte form. The relationship of the immature cellular cytology in oligodendrogliomas can be understood when the presence of glioblasts or spongioblasts is evaluated. The latter cells appear to initiate the tumor growth and are the precursors of the oligodendroblasts, which, in turn, appear to have the tendency to develop astroblasts and astrocytes; these, then, form oligodendroastroblastomas and oligodendroastrocytomas, protoplasmic or fibrillary, respectively.

These tumors arise in early middle life, have a longer course of symtoms than do other gliomas, and are principally located in the cerebral hemispheres, the frontoparietal lobe being most frequently affected.

SIEKERT, Rochester, Minn.

Meninges and Blood Vessels

A CASE OF PERSISTENT CAROTID-BASILAR ANASTOMOSIS ASSOCIATED WITH ANEURYSM OF THE HOMOLATERAL MIDDLE CEREBRAL ARTERY MANIFESTED BY OCULOMOTOR PALSY. F. MURTAGH, H. STAUFFER, and R. HARLEY, J. Neurosurg. **12**:46, 1955.

The authors report a case of aneurysm of the left middle cerebral artery associated with a persistent carotid-basilar anastomosis. The patient was a 62-year-old white man who was seen because of double vision and pain above the left eye. Neurological examination revealed ptosis of the left eyelid with impairment of upward, downward, and lateral movements of the left eye. The pupillary responses and corneal reflexes were normal. By means of left carotid arteriography with 30% sodium acetrizoate (Urokon), a persistent carotid-basilar anastomosis with a left middle cerebral aneurysm was noted. The aneurysm was then trapped and ligated by a surgical approach. Although expressive aphasia and focal Jacksonian seizures occurred postoperatively, the patient had no diplopia, aphasia, or headache when examined 18 months later.

The authors believe this aneurysm is of congenital origin, and they are unable to explain the occurrence of the oculomotor palsy without involvement of the pupillary fibers.

MANDEL, Philadelphia.

Diseases of the Brain

BENIGN FORMS OF INTRACRANIAL HYPERTENSION—"TOXIC" AND "OTITIC" HYDROCEPHALUS. J. FOLEY, Brain **78**:1, 1955.

Foley reports 60 cases of proved intracranial hypertension in the absence of a space-occupying lesion. In each case, the ventricles were shown by ventriculography to be normal or smaller than normal in size and normal in shape. Furthermore, the ventricular size did not vary with the pressure or the duration of the illness. The significance of a normal ventricular system under increased pressure is explained upon the basis of the Monro-Kellie hypothesis. When the ventricle is obstructed, its dilatation takes place at the expense of the cerebral vascular bed and the fluid over the convexity of the hemispheres. If the cerebrospinal fluid pathways are obstructed outside the brain, as by thrombophlebitis of the sagittal sinus, the ventricles and subarachnoid space will increase at the expense of the vascular bed alone. However, if the venous outlet is obstructed, there can be no compression of the vascular bed, and the ventricles will therefore

be normal, or smaller than normal, in size. The latter situation exists in thrombosis of the superior sagittal sinus. The author believes, therefore, that the term hydrocephalus is inappropriate when applied to the latter condition and that the term "benign intracranial hypertension" is most applicable.

The author divides his cases into three main groups. The first group consisted of the otitic cases, in which thrombosis of the major lateral sinus was the cause, following otitis media, mastoidectomy, or perisinus abscess. The second, or larger, group occurred almost exclusively in females, predominantly in the fourth decade, without any history of infection or head injury. Obesity was a common feature of this group and was occasionally associated with pregnancy or miscarriage. Headache, neck stiffness, and progressive loss of vision with scotomata were the commonest symptoms and signs. Vision was lost earlier in these cases than in papilledema due to cerebral tumors. The third group occurred equally in males and females of a younger age group and usually followed a head injury or a mild infection. There is little evidence that thrombosis of the superior sagittal sinus is the cause of intracranial hypertension in the second and third groups. The electroencephalogram in these cases does not show the slow activity that is commonly seen in increased intracranial pressure due to cerebral tumors. There is evidence that slow activity, if present in these cases, is due to a fall in the cerebral blood flow. Estimation of cerebral blood flow in three cases of benign intracranial hypertension was found to be at the upper limit of normal.

MANDEL, Philadelphia.

Diseases of the Spinal Cord

MULTIPLE OPERATIONS FOR PROTRUDED LUMBAR INTERVERTEBRAL DISK. J. H. KELLEY, K. C. VORIS, H. J. SVIEN, and R. K. GHORMLEY, Proc. Staff Meet., Mayo Clin. **29**:546, 1954.

Kelley and his associates studied the results of treatment in a group of 54 patients who had had two unsuccessful operations for protruded lumbar intervertebral disc. Subsequent to the two unsuccessful operations, 27 of these patients were treated by conservative measures, and the other 27 underwent a third operation.

Conservative treatment consisted of adequate back support, use of a firm mattress, physical therapy, and limitation of certain activities. Acceptable improvement was obtained in 14 of the 27 patients treated conservatively, and no improvement occurred in the remaining 13 so treated.

Most of the patients with sciatic pain went on to the third operation. Of the 27 patients who underwent a third operation, 15 had protruded discs, which were removed; in these 15 patients 16 fusions were performed, with the following results: good, 6 cases; fair, 5 cases, and poor, 5 cases. In the other 12 patients treated surgically no protruded discs were found, but in some of these cases adhesions surrounding the nerve roots were noted. In these 12 patients the end-results are noted as being good in 2 cases, fair in 3 cases, and poor in 7 cases.

In summing up their observations on the possible causes of failure in such cases, the authors point to (1) nerve root adhesions, (2) failure of bone grafts, (3) adhesive arachnoiditis set up by various intraspinal contrast media, (4) recurrent protrusion of a disc, and (5) postoperative infections. It is also pointed out that psychoneurosis plays a role in the failures, and that the element of compensation plays a part in some of these cases.

ALPERS, Philadelphia.

GASTRIC ATROPHY WITH SUBSEQUENT PERNICIOUS ANEMIA AND PRONOUNCED SUBACUTE COMBINED DEGENERATION OF THE CORD. E. G. ROBERTSON, I. J. WOOD, and R. A. JOSKE, Lancet **2**:69, 1955.

Robertson and his co-workers report on an elderly patient whose first complaint was dyspepsia and who had minimal subjective neurological symptoms. Gastric biopsy revealed complete gastric atrophy. When first investigated, the peripheral blood and bone marrow showed no evidence of megaloblastosis. The dysesthesias suggested a diagnosis of subacute combined degeneration of the cord, but it was impossible to state that the patient did not have mild peripheral neuritis, even though achlorhydria was present. The picture in this patient was unchanged for five years, during which time he was given no therapy. He then developed typical symptoms and signs of both pernicious anemia and subacute combined degeneration of the cord. At this point treatment was instituted. There was rapid response to treatment with cyanocobalamin.

This patient thus provides evidence which strengthens our belief that gastric atrophy precedes the development of both pernicious anemia and subacute combined degeneration of the cord in their florid forms.

YASKIN, Camden, N. J.

NERVOUS DEGENERATION IN MALIGNANT DISEASE. W. T. E. MCCAUGHEY and J. H. D. MILLAR, Lancet **2**:365, 1955.

McCaughey and Millar report an unusual type of neurological disorder in association with a bronchial carcinoma which had not metastasized to the nervous system. The patient had weakness of the arms, particularly of the hand grip, but the tone was normal. The small muscles of both hands were moderately wasted. The legs were rigid in extension. Very slight passive movements were possible below the knees, but caused pain. All the tendon reflexes were absent. Vibratory perception was absent in all limbs and in the trunk up to the clavicles. Muscle-joint sensation was slightly impaired in the fingers. The patient had extensor spasms of the legs. Necropsy revealed a neoplasm in the lower lobe of the right lung, which on microscopic examination proved to be an anaplastic carcinoma of the oat-cell type. In the spinal cord, demyelination was present in the posterior columns, the posterolateral columns, and the posterior nerve roots. No myelin degeneration was demonstrated elsewhere in the cord. There was no evidence of damage to nerve cells in the cord, the brain, or the cerebellum. Porphobilinogenuria was present.

The authors suggest that the degenerative process responsible for these disturbances has a predilection for certain well-defined parts of the nervous system, producing such conditions as sensory neuropathy and myopathy, mixed motor and sensory neuropathy, subacute cortical cerebellar degeneration, and proximal motor neuropathy. These conditions have been reported in pure form but often occur in various combinations. Little is known about their etiology.

YASKIN, Camden, N. J.

Treatment, Neurosurgery

RESULTS OF TREATMENT OF HUNTINGTON'S CHOREA WITH PROCAINE AMIDE HYDROCHLORIDE. J. A. LAZARTE, C. W. BAARS, and J. S. PEARSON, Am. J. M. Sc. **229**:676, 1955.

Three patients with Huntington's chorea with severe motility disturbance, but without comparable intellectual impairment, were studied to ascertain the degree of their dexterity in executing standardized tasks. Two subjects were then given procainamide hydrochloride U. S. P. (Pronestyl Hydrochloride) for 35 days, and the third was given a placebo. There was no significant change in dexterity or in the chorea in any of the patients tested.

BERLIN, New York.

AQUEDUCT STENOSIS: CLINICAL ASPECTS AND RESULTS OF TREATMENT BY VENTRICULOCISTERNOSTOMY (TORKILDSEN'S OPERATION). KENNETH W. E. PAINE and WYLIE MCKISSOCK, J. Neurosurg. **12**:127, 1955.

Occlusion of the aqueduct of Sylvius may be caused by congenital malformation, postinflammatory ependymitis, neoplasms, or aneurysms. One method of overcoming this obstruction was devised by Torkildsen, who provided a new Sylvian aqueduct by passing a soft rubber tube from one lateral ventricle through a subgaleal tunnel over the occiput and into the lower end of the cisterna magna.

Paine and McKissock report their observations in a series of 24 cases treated by the Torkildsen method for non-neoplastic aqueduct obstruction. Symptoms developed before the age of 20 years in approximately two-thirds of the patients, the shortest duration of complaints being 3 weeks and the longest 46 years. Headache was the commonest symptom. It was bifrontal or bitemporal, was worse in the morning, was aggravated by exertion, and cleared during the day. It was frequently accompanied by nausea and vomiting. Visual impairment and mental changes were noted in 11 cases, unsteadiness of gait, double vision, and seizures comprising the remainder of the symptoms. The objective findings included evidence of papilledema, in 21 cases, diminished visual acuity, nystagmus, increased head size, and pyramidal tract signs. Roentgenograms of the skull demonstrated raised intracranial pressure in 20 cases, with erosion of the dorsum sellae and digital markings of the vault. Large diploic channels were noted in the occipital bone over the posterior fossa. With benign obstructions in childhood, there was a greater relative enlargement

of the supratentorial portion of the skull than when the obstruction was in or below the fourth ventricle, where the posterior fossa would be enlarged by the tumor and the supratentorial portion would be enlarged by hydrocephalus. The authors performed ventriculograms with iophendylate (Myodil; Pantopaque) in 12 cases in order better to visualize the obstruction of the aqueduct. With this method the obstructed aqueduct appeared to be occluded, had a bulbous or funneled shape, or was noted to be atresic.

The short-circuit operation was successful in 18 cases (73%), although successful economic results were obtained in only 9 out of 21 followed for more than a year. There were five postoperative deaths in the series. The authors conclude that hydrocephalus caused by aqueduct stenosis can be relieved by this shunt operation but visual deterioration is unlikely to be reversed by the procedure. With earlier diagnosis, the late results of this procedure may be improved as the shunt operation is successful in most cases.

MANDEL, Philadelphia.

RESULTS OF DIRECT ATTACK ON NON-FISTULOUS INTRACRANIAL ANEURYSM, WITH REMARKS ON STATISTICS. CARL GRAF, J. Neurosurg. **12**:146, 1955.

Graf reports his results of surgery in 55 cases of intracranial aneurysms. This series included all patients upon whom surgery was performed as soon as the diagnostic methods were completed. The aim was to reduce the mortality and possibility of early recurrent hemorrhages, which was commonest in the second and third weeks after the initial rupture.

In the 55 cases there was an over-all mortality of 45%. Intracerebral hematomas occurred in 16 patients, 14 of whom died after surgery. The hematomas were associated with the anterior communicating or anterior cerebral artery in nine cases and with the middle cerebral artery in five cases. These cases had the highest mortality. The initial neurological deficit revealed that nine patients were hemiplegic, four were in coma, and four had papilledema. Most of these patients died.

The author concludes that operation for intracranial aneurysm should be deferred, if possible, three weeks after the initial subarachnoid hemorrhage. The mortality of operation within this period is as great as when the disease is allowed to follow its natural course. A high percentage of patients will die in the early period following subarachnoid hemorrhage, with or without surgery. In cases of supraclinoid aneurysms, in which the incidence of hematoma is low, recovery is much higher. Carotid ligation, hypotensive drugs, and sympathetic blocking agents to reduce vasospasm offer little reassurance that the patient can be protected from a recurrent fatal hemorrhage before the optimal time for surgery.

MANDEL, Philadelphia.

OBSERVATIONS ON VENTRICULAR AND LUMBAR SUBARACHNOID PERITONEAL SHUNTS IN HYDROCEPHALUS IN INFANTS. MICHAEL SCOTT, HENRY WYCIS, FREDERICK MURTAUGH and VICTOR REYES, J. Neurosurg. **12**:165, 1955.

The authors report their results with ventriculoperitoneal and lumboperitoneal shunts in the treatment of progressive hydrocephalus in 32 infants. They noted that the operative procedure was well tolerated in all cases and the operative mortality was 5%. Surgical results were better in the 22 cases of communicating hydrocephalus than in the noncommunicating type. In this series a stainless steel button was suspended into the peritoneal cavity and the extraperitoneal portion connected to a rubber tube which was placed in the ventricle or subarachnoid space. It was found that the rubber tubing was superior to plastic tubing, since the latter has the disadvantage of kinking when bent and becomes brittle when in contact with the spinal fluid over a long period of time. The rubber tube was well tolerated in the ventricles, and only a slight capsular reaction was noted in the subcutaneous tissues of the skin. The stainless steel button was satisfactory in only 50% of the cases, being frequently obstructed by omentum. The authors conclude that the shunt operations should not be abandoned, since the operative mortality is low and lives may be prolonged.

MANDEL, Philadelphia.

PERITONEAL SHUNTS IN THE TREATMENT OF HYDROCEPHALUS AND INCREASED INTRACRANIAL PRESSURE. IRA J. JACKSON and S. R. SNODGRASS, J. Neurosurg. **12**:216, 1955.

Jackson and Snodgrass report their results in the treatment of increased intracranial pressure in 62 patients over a four-year period. The ages varied from 3 days to 65 years, but the majority were under 14 years of age. The patients were treated by ventriculoperitoneal or by lumbar

subarachnoid shunts. The complications were many, but blockage of the tube within the abdominal cavity by either omentum or scar tissue occurred most frequently. Obstruction by small amounts of cerebral tissue were less frequent in the cranial portion of the tube. Postoperative infection, kinking of the tube, and hypotensive headaches were the other complications encountered.

The more successful shunts were in patients with a diagnosis of infantile hydrocephalus or pseudotumor cerebri. Only 24 patients in this series had shunts which functioned over one year, and the longest was a single shunt which had functioned four years, at the time of the report. The authors state from their experience that the longer these patients are followed, the poorer are the long-term results. Shunt operations have a very definite, but limited, value in the neurosurgeon's armamentarium.

MANDEL, Philadelphia.

MESTINON IN THE TREATMENT OF MYASTHENIA GRAVIS. M. R. WESTERBERG and K. R. MAGEE, Neurology **4**:762, 1954.

Twenty-two patients with myasthenia gravis were given Mestinon bromide. Their ages ranged from 17 to 64 years; there were 16 female and 6 male patients. The longest period of observation was seven months and the shortest three months. Symptoms ranged from mild to severe in various patients. The maintenance dose of Mestinon ranged from 90 to 900 mg. a day. Most patients found that 60 mg. of Mestinon was equivalent to 30 mg. of neostigmine; they therefore used about half as many tablets of Mestinon.

Twenty-one, or 95% of the patients preferred Mestinon to neostigmine. It gave more prolonged effect and an evener maintenance of strength than did neostigmine. Side-effects or toxic reactions were minimal. Mestinon was effective given either alone or in conjunction with ephedrine, potassium, or tetraethylpyrophosphate.

ALPERS, Philadelphia.

STUDIES IN CEREBROVASCULAR DISEASE: III. USE OF ANTICOAGULANT DRUGS IN TREATMENT OF INSUFFICIENCY OR THROMBOSIS WITHIN THE BASILAR ARTERIAL SYSTEM. C. H. MILLIKAN, R. G. SIEKERT, and R. M. SHICK, Proc. Staff Meet., Mayo Clin. **30**:116, 1955.

The patients in this series selected for treatment with anticoagulants were carefully chosen. Two groups were included: (1) patients (5) with intermittent insufficiency of the basilar system, and (2) patients (21) with thrombosis within the basilar arterial system. Each case is briefly summarized. Review of the case summaries demonstrates that these patients constitute a special group. It is emphasized that patients with acute massive cerebral infarction (patients with the ordinary "stroke") were not treated with anticoagulant drugs.

During the treatment, in all instances, the attacks suffered by the five patients in the first group ceased. Three patients of the second group died, giving a mortality rate of 14% for this group. The mortality rate for a group of untreated patients was 43%.

The length of time anticoagulant drugs should be administered is not known.

The authors emphasize the fact that the general danger of anticoagulant therapy was carefully assessed in each case, and the use of such treatment sharply limited to specific categories of intracranial vascular disease. It is their impression that anticoagulant drugs are indicated in the treatment of insufficiency or thrombosis within the basilar artery system as soon as a diagnosis of this type of intracranial vascular disease can be established.

ALPERS, Philadelphia.

News and Comment

PERSONAL NEWS

New York State Psychiatric Institute.—On the afternoon of Thursday, Oct. 27, an oil portrait by Soss Melik of Dr. Nolan D. C. Lewis was presented by Commissioner Paul Hoch to the New York State Psychiatric Institute in the name of the Department of Mental Hygiene of the State of New York.

Dr. Lewis was for 17 years, until his retirement, in 1953, Director of the Psychiatric Institute and Professor of Psychiatry of the College of Physicians and Surgeons.

The staff and employees of the Institute, the Directors of the hospitals of the New York State Department of Mental Hygiene, and the members of the Department of Psychiatry of Columbia University were invited to be present at the reception held in Dr. Lewis' honor and for the presentation of the portrait.

ANNOUNCEMENTS

A. M. A. Annual Meeting, Chicago, June 11-15, 1956.—The 105th Annual Meeting of the American Medical Association will be held in Chicago, June 11-15, 1956, with a full program of lectures, television, motion pictures, and scientific exhibits.

The lecture program for each Section is prepared by the Section Secretary, and prospective participants should communicate as soon as possible with the Secretary of the Section before which they hope to read a paper. Application blanks for space in the Scientific Exhibit are now available and may be obtained from the Section Representative to the Scientific Exhibit.

Section on Nervous and Mental Diseases

Secretary: Karl O. Von Hagen, M.D., 2010 Wilshire Blvd., Los Angeles 57.

Exhibit Representative: G. Wilse Robinson Jr., M.D., 2625 W. Paseo, Kansas City 8, Mo.

Additional information may be obtained from the Secretary, Council on Scientific Assembly, American Medical Association, 535 N. Dearborn St., Chicago 10.

GENERAL NEWS

University of Minnesota Continuation Course.—Neurology will be the subject of a continuation course to be presented by the University of Minnesota at the Center for Continuation Study Feb. 6 to 10, 1956. Intended primarily for physicians in general practice, the program will have appeal also to neurologists and neurosurgeons. The most commonly seen neurological symptoms and syndromes will be stressed.

Guest faculty will include Dr. William M. Meacham, Associate Clinical Professor of Surgery, Vanderbilt University School of Medicine, Nashville; Dr. Morris B. Bender, Director, neurology service, Mount Sinai Hospital, and Professor of Clinical Neurology, New York University College of Medicine, New York; Dr. John F. Sullivan, Associate Professor and Head, Department of Neurology, Tufts College Medical School, Boston, and Dr. Oliver H. Lowry, Professor and Head, Department of Pharmacology, Washington University School of Medicine, St. Louis.

The course will be presented under the direction of Dr. A. B. Baker, Professor and Director, Division of Neurology, and Dr. William T. Peyton, Professor and Director, Division of Neurosurgery, University of Minnesota Medical School. Lodging and meal accommodations are available at the Center for Continuation Study.

National Mental Health Act Grants.—The National Institute of Mental Health, Public Health Service, U. S. Department of Health, Education, and Welfare, announces Dec. 15, 1955, as the closing date for the year beginning July 1, 1956, for filing applications for grants under the National Mental Health Act in support of training programs in psychiatry, clinical psychology, psychiatric social work, and psychiatric nursing. Applications may also be made by university training centers for the support of career teacher programs for the preparation of teaching personnel in the mental health disciplines.

The deadline date for filing applications for the support of pilot and evaluation studies proposing new methods of teaching, or evaluation of teaching and training methods in the mental health disciplines, is Jan. 15, 1956.

Application forms and details regarding the types of support available may be obtained from the Chief, Training and Standards Branch, National Institute of Mental Health, National Institutes of Health, Bethesda 14, Md.

Western Regional Research Symposium.—In cooperation with the American Psychiatric Association, the Department of Psychiatry of the University of California School of Medicine at Los Angeles and the University of California University Extension have announced plans for a two-day Western Regional Research symposium on the "Application of Basic Science Techniques to Psychiatric Research," to be held in Los Angeles in January, 1956.

Norman Q. Brill, M.D.; Donald B. Lindsley, Ph.D., and Charles W. Tidd, M.D., head a planning committee for the program on Jan. 26 and 27. Throughout the two-day symposium, sessions will be held in Room 2147 of the U. C. L. A. Life Sciences Building.

The course is open to psychiatrists, psychologists, psychiatric social workers, psychiatric nurses and others with the consent of the course chairman, according to Thomas H. Sternberg, M.D., assistant Dean for Postgraduate Medical Education at U. C. L. A. The conference will convene at 9:30 on the first morning, with U. C. L. A. Chancellor Raymond B. Allen, M.D.; Stafford L. Warren, M.D., Dean of the School of Medicine, and Dr. Sternberg making the welcoming remarks. During ensuing sessions topics will include Brain Mechanisms and Behavior, Experimental Studies of Psychosomatic Disease, Methods of Blocking Neuroendocrine Mechanisms, Brain Metabolism, and numerous related subjects.

Requests for information and registration blanks should be addressed to Dr. Thomas H. Sternberg, University of California School of Medicine, Los Angeles 24. Fee for the symposium is $3.50, made payable to the Regents of the University of California. A cocktail party at the Beverly Hills Hotel for all who attend, including wives, is set for 7 p. m. on Jan. 26.

American Board of Psychiatry and Neurology, Inc.—At the October, 1955, meeting of the American Board of Psychiatry and Neurology, Inc., the following requirements were adopted:

1. All applicants who wish to qualify for examination for certification in psychiatry or neurology under the regulations relating to training credit and who began training on or after July 1, 1956, must show that at least 24 months of their residency training have been secured in residency training programs approved for at least two years of residency training in the specialty in which they seek certification.

2. Because of an increase of all expenses in conducting the examination, the following fee schedule will be in effect as of Jan. 1, 1956:

(*a*) Application fee...$50.00

(*b*) Examination fee...$75.00

(*c*) Complete reexamination fee...$75.00

(*d*) Partial reexamination fee...$50.00

American Academy for Cerebral Palsy.—At the meeting of the American Academy for Cerebral Palsy, Memphis, Oct. 10, 11, and 12, the following officers were elected for the forthcoming year:

Dr. Margaret Jones, president
University of California Medical Center
Los Angeles

Dr. Nicholson J. Eastman, president-elect
Johns Hopkins Hospital
Baltimore

Dr. Robert A. Knight, secretary-treasurer
869 Madison Ave.
Memphis

The 1956 meeting will be held in Chicago; the 1957 meeting will be held in New Orleans.

New York State Psychiatric Institute.—Dr. Leon Roizin has been appointed Principal Research Scientist, Neuropathology, Sept. 16, 1955, at the New York State Psychiatric Institute, to succeed Dr. Armando Ferraro who retired last year.

Dr. I. Herbert Scheinberg has resigned his position as Principal Research Scientist, Internal Medicine, as of Oct. 31, 1955, to accept the post of Associate Professor of Medicine at the Albert Einstein School of Medicine.

Dr. Bernard C. Holland has been appointed to fill this post, effective Nov. 1, 1955.

Books

What Is Creative Thinking? By Catharine Patrick, Ph.D. Price, $3. Pp. 210. Philosophical Library, Inc., 15 E. 40th St., New York, 1955.

This book is an attempt to collect in one volume the available information now in print about creative thinking, in order to provide a comprehensive view and critical evaluation of this mental process. There is an extensive bibliography, and a large proportion of the text consists of selected quotations. Each chapter is conveniently summarized.

Steps in creative thinking are delineated and summarized as follows: (1) preparation, with deliberate and nondeliberate mental activity, and a feeling of doubt and perplexity; (2) incubation, (3) illumination, with spontaneous appearance of a new idea, associated with feelings of confidence and pleasure, and (4) verification or revision, associated with a fully conscious comparison of the new idea with established ones.

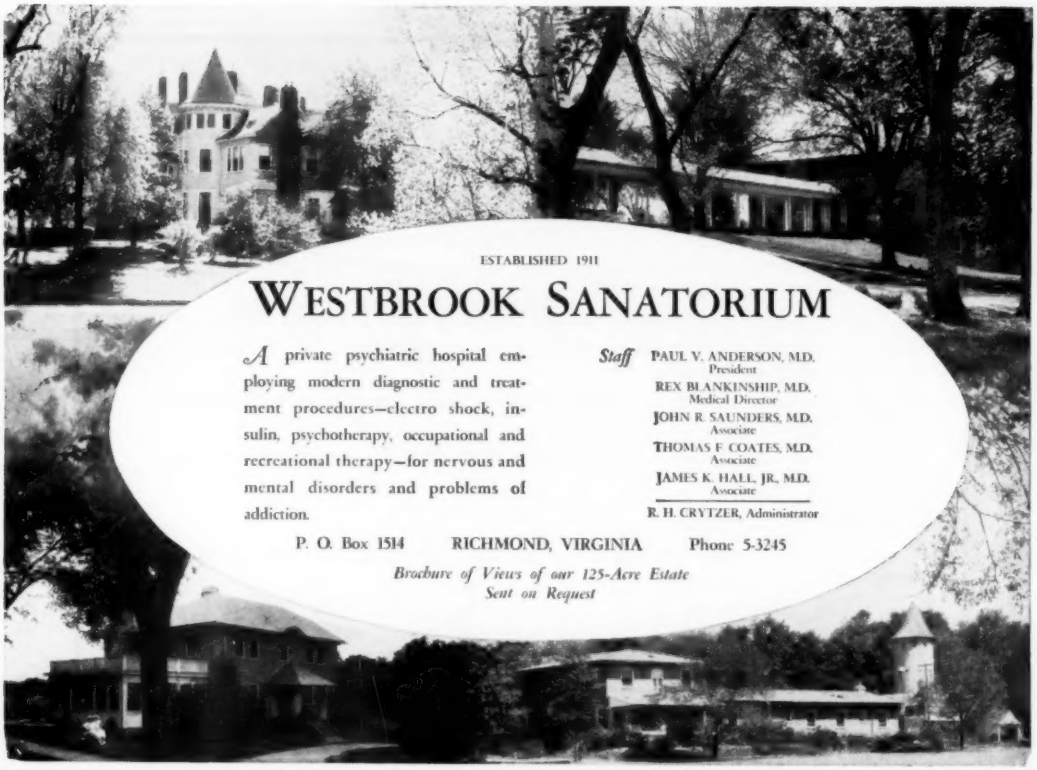
Psychotic thought and ordinary (normal) reverie are seen as lacking in verification and revision. Problems to be solved may be compared to nervous system disequilibrium, with the solution providing restoration to the steady state. Creative thinking is seen as the same fundamental process no matter what the field of endeavor may be.

The author lists favorable conditions for creative thought, including relatively unlimited time, adequate information, knowledge of the culture, attention, optimism, sense of humor, motivation, appropriate mood, periods of idleness and reverie, relaxation of routine, and a relative freedom from rigid habits. She concludes with suggestions for stimulating creative thinking in the home and the classroom.

This volume will be of interest primarily to psychologists, teachers, and students of aesthetics.

Sexuelle Konstitution. By Helene Stourzh-Anderle. Price, $6.25. Pp. 262. Wilhelm Maudrich, Wien, 1955.

This is the first of a series of the "Vienna Contributions to Research in Sex," published by the recently formed "Austrian Association for Research in Sex" and edited by Dr. W. F. Brix. The volume represents a very thorough investigation of this problem, based on 829 literary sources, of which 12 are the author's own. In the chapter entitled "Sexuality," the author studies the hormones and drives, their development in the individual, and their deviations. She considers a person "intersexual" if in his personality (body and soul) there coexist separate male and female characteristics. In the sexual constitutional types, she characterizes the normal man (and the virile woman) as large, bony, and sturdy; the feminine man (and normal woman) as medium large, medium fat, and medium sturdy; the infantile man (and the infantile woman) as small, delicate, and youthful; the child (and puerile woman) as small and youthful. The parasexuals may be classified under three headings: the intersexuals (feminine men and virile women), subsexuals (infantile men and infantile women), and intersubsexuals (feminine-infantile men and virile-infantile women). She investigates the role of sexuality in mental illnesses, criminality, and genius. At the end, she gives a "sexual" biographical list of persons famous in history who were abnormal or maladjusted in their sexual drives or suffered from various psychopathological disturbances. The study is exhaustive and is well documented.



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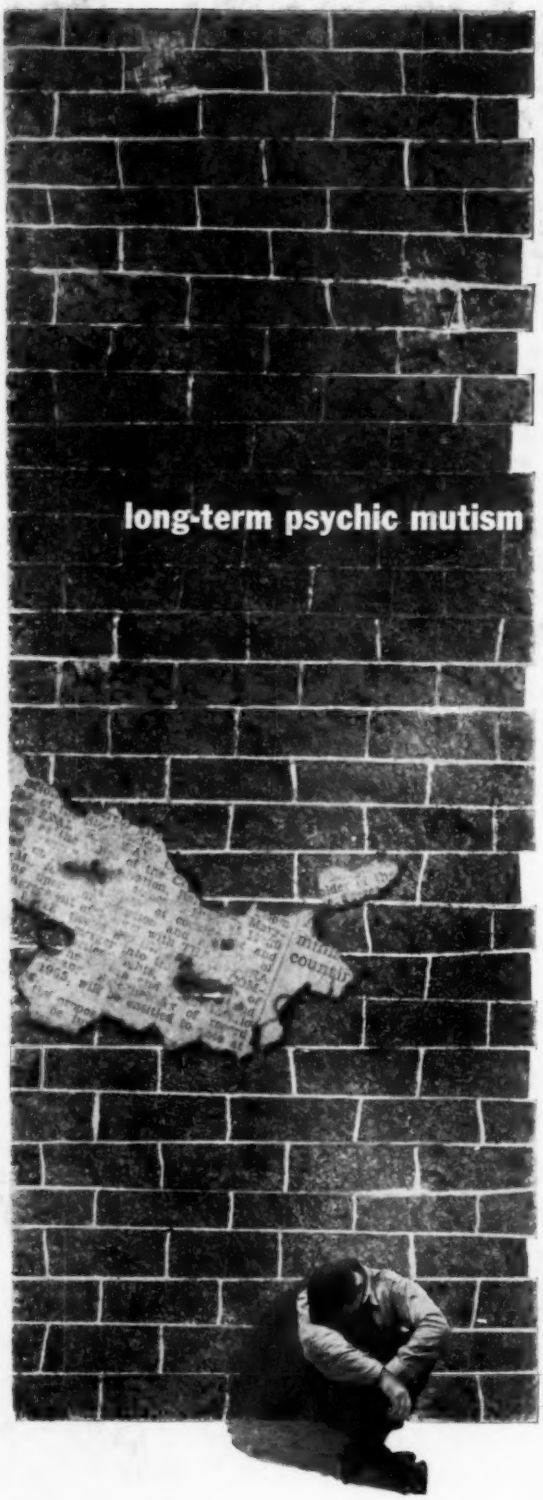

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